Fatigue after Liver Transplantation

Berbke van Ginneken

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The concept of the cover design is energy. It shows energy, or lack of energy in its broadest definition. From energy in human beings to energy waves, flows, and lines. But also energy as a natural phenomenon as shown in the background of the + signs; a photograph of the polar light.

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Fatigue after Liver Transplantation
Vermoeidheid na levertransplantatie

Proefschrift

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Chapter 1

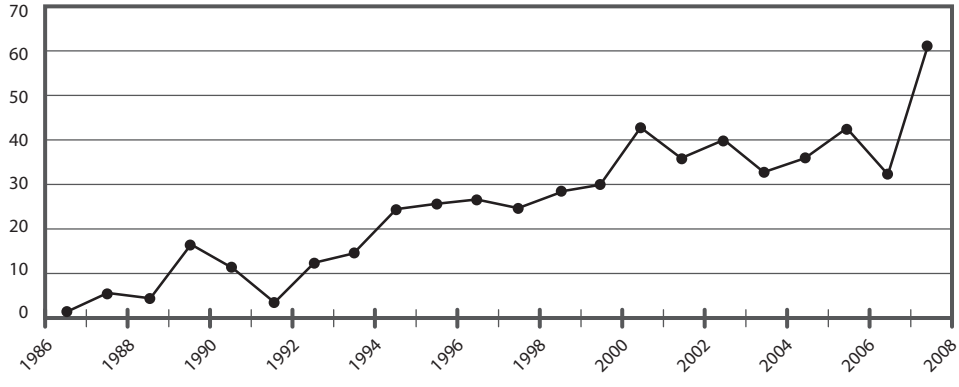
General introduction

Liver transplantation

Liver transplantation (LTx) has developed from an experimental procedure in the 1960's to the preferred treatment for end-stage liver disease nowadays. The first human LTx was performed by Starlz and his team in 1963 in Colorado.[1] Unfortunately, this patient died within a few days. The first successful LTx was performed in 1967 by the same team; this patient survived one year. The most prevalent indications for LTx in Europe are virus-related cirrhosis (22%), alcoholic cirrhosis (19%), cancer (18%), cholestatic liver diseases (11%), acute hepatic failure (9%) and metabolic disease (6%).[2]
The main complications in the immediate postoperative period are dysfunction and rejection of the graft, infections, bile duct complications and pulmonary or neurological problems. Long-term complications after LTx are typically a consequence of the prolonged immunosuppressive therapy, and include diabetes mellitus, infections, renal dysfunction, hypertension, osteoporosis, and de novo neoplasia.[3]

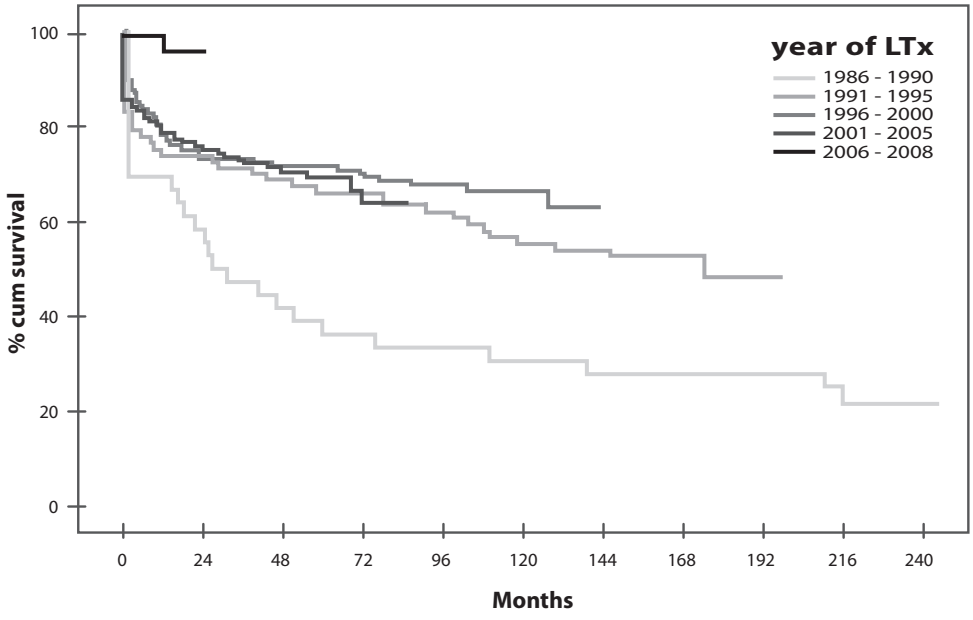
Currently, three University Medical Centers are performing LTx's in the Netherlands: Groningen, Leiden and Rotterdam. The total number of performed LTx's in the Netherlands in 2007 was 149, of which three were living-donor LTx's.[4] Since 1986, almost 500 patients received a new liver in the Erasmus University Medical Center Rotterdam, with a peak of 61 LTx's in 2007 (see Figure 1).

Figure 1. Number of performed liver transplantations per year in Rotterdam.
Source: Database LTx Erasmus University Medical Center.



Over the past decades, patient survival after LTx has improved markedly, due to improved technical expertise, better selection of patients, improved post-LTx management of complications, and improved immunosuppressive therapy. In Rotterdam, LTx has achieved 1-year and 10-year patient survival rates of respectively, 95% and 65% (see Figure 2).

Figure 2. Patient survival according to the year of transplantation.
Source: Database LTx Erasmus University Medical Center.



Recently, researchers have shifted focus to prevent long-term complications and improve health-related quality of life (HRQoL) after transplantation.[5, 6] HRQOL refers to those aspects of quality of life that are directly related to health and are potentially affected by the health care system. Most studies on HRQoL after LTx report that although HRQoL improves markedly after LTx, patients show considerable deficits compared to the healthy population.[6] According to several HRQoL studies, it appears that fatigue is one of the most common symptoms in patients after LTx.[7, 8]

Fatigue

In the literature, fatigue is generally described and measured as a multidimensional phenomenon, indicating both experienced fatigue and physiological fatigue.[9] Experienced fatigue is usually defined as an overwhelming sense of tiredness, lack of energy and feelings of exhaustion. In physiology, fatigue is usually defined as the loss of voluntary force-producing capacity during exercise. This loss can have a peripheral and a central origin, depending on whether it is found to originate in the muscle tissue or in the nervous system.[10] Fatigue can be acute or chronic. Acute fatigue usually has an identifiable cause, typically occurs in healthy persons and is relieved by appropriate rest. Studies on possible causes of chronic fatigue are abundant but inconclusive. Chronic fatigue often accompanies medical illness, lasts longer than six months, often has multiple or unknown causes, usually is poorly relieved by rest, and typically is not related to exertion.[11]

Chronic fatigue is a common complaint among patients with chronic disease, such as multiple sclerosis, systemic lupus erythematosus, liver diseases, rheumatoid arthritis and cancer survivors.[12-18] Prevalence of fatigue in these chronic diseases ranges from 17 to 68%.[12-18] In this thesis, when we report on 'fatigue', we mean chronic experienced or self-perceived fatigue. According to The Brighton Collaboration Fatigue Working Group, "fatigue is a perception of a lack of energy, or a feeling of tiredness that affects mental and physical activity, which differs from sleepiness or lack of motivation. Fatigue may be aggravated by, but is not primarily attributed to, exertion or diagnosable disease".[19] This definition explains that fatigue as a chronic symptom is not relieved by a good night's sleep. The prevalence of chronic fatigue within the general population is unclear.

Fatigue is difficult to measure, because it is subject to variable perception by the same subject over time, and of variable meaning and significance between subjects. To allow comparison between persons, the experienced fatigue needs to be quantified.[10] Often used self-report questionnaires measuring fatigue are the Fatigue Severity Scale (FSS), a visual analogue scale for fatigue (VAS-fatigue), the Multidimensional Fatigue Inventory (MFI-20), and the Checklist Individual Strength (CIS-20).[20-24] The FSS is a widely used fatigue questionnaire, particularly in multiple sclerosis, but also in liver diseases such as primary biliary cirrhosis and chronic hepatitis C.[14, 21, 25] It consists of 9 items measuring the impact of fatigue on specific types of functioning. The VAS-fatigue is a simple method to measure the severity of fatigue on

a continuous scale. The VAS-fatigue has shown to have a higher sensitivity to change in levels of fatigue as compared to longer more complex fatigue instruments.[26]
The MFI-20 and the CIS-20 consist of 20 items measuring various dimensions of fatigue. The MFI-20 consists of five scales: *general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue*. The CIS-20 consists of four scales for the fatigue dimensions *severity of subjective feeling of fatigue, concentration, motivation, and physical activity*. In this thesis we only used the fatigue dimension *severity of subjective feeling of fatigue*. The MFI-20 and the CIS-20 have the same origin and are both used in the Netherlands. Throughout this thesis we changed from using the MFI-20 to the use of the CIS-20, because the CIS-20 is more frequently used in Dutch studies on chronic fatigue and more reference values are available.

Fatigue after liver transplantation

The observation of medical specialists that LTx recipients often experience fatigue, gave rise to the research project described in this thesis. Previous studies reported that, although the intensity of fatigue was reduced after LTx, fatigue remained the most distressing symptom one year after LTx.[8, 27] However, studies about prevalence of fatigue after LTx are lacking. Rehabilitation programs might be effective in reducing severity of fatigue after LTx. However, knowledge of the factors associated with fatigue after LTx is necessary for the development of fatigue-reducing interventions.
Aadahl et al. suggested that fatigue after LTx is primarily physical, rather than psychological.[7] People with disabilities or chronic diseases often have a low physical fitness and an inactive lifestyle, which may be related to fatigue.[28] Physical exercise programs are widely reported to favourably impact fatigue in healthy persons and in patients with chronic illnesses.[29-33] There have been no studies examining the effect of rehabilitation on fatigue in LTx recipients. It is possible that LTx recipients experience a cycle of fatigue leading to inactivity, which leads to a reduction in physical fitness, which in turn leads to more fatigue. By breaking this cycle of fatigue, inactivity, and deconditioning, intervention programs may help to reduce the problem of fatigue. This hypothesis formed the background of this thesis.

Aims and outline of the thesis

The studies presented in this thesis aim to explore the severity of fatigue among LTx recipients and its relations to physical fitness and level of daily physical activity (PA). We also studied whether severity of fatigue was associated with personal and medical factors, HRQoL, daily functioning, sleep quality, anxiety and depression. Furthermore, we studied the feasibility and effect of a rehabilitation program, which aimed at improving physical fitness and daily PA, on fatigue, physical fitness, daily PA, daily functioning, participation and HRQoL in fatigued LTx recipients.

Chapter 2 describes the prevalence of fatigue among LTx recipients transplanted at the Erasmus University Medical Center. In this cross-sectional study, we also studied associations between fatigue on the one hand and age, gender, indication for transplantation, time since transplantation, immunosuppressive medication, daily functioning and HRQoL on the other.

Chapter 3 focuses on the longitudinal assessment of fatigue, daily functioning and HRQoL in LTx recipients during a two-year period and explores whether changes in fatigue are associated with changes in daily functioning and HRQoL. Furthermore, we determined whether sleep quality, anxiety, and depression were associated with fatigue.

Chapter 4 describes the level of daily PA of LTx recipients, and studies associations with fatigue and HRQoL to gain insight into the role of daily PA in the severity of fatigue and HRQoL in LTx recipients.

Chapter 5 describes the aerobic capacity, muscle strength and body composition of LTx recipients, and studies associations with fatigue and HRQoL to gain insight into the role of physical fitness in the severity of fatigue and HRQoL in LTx recipients.

Chapter 6 explores the feasibility and effect of a rehabilitation program, which aimed at improving physical fitness and daily PA, on fatigue in fatigued LTx recipients.

Chapter 7 explores the effect of the abovementioned physical rehabilitation program on daily functioning, participation, and HRQoL in fatigued LTx recipients.

Chapter 8 addresses the main findings of the thesis, discussing the strengths and weaknesses of the aforementioned studies, the clinical implications and suggestions for future research.

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Chapter 2

Fatigue is a major problem after liver transplantation

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Liver Transplantation, 2006; 12: 928-933

Abstract

Objective Fatigue is often experienced after liver transplantation. The aim of this cross-sectional study was to assess the severity of fatigue in liver transplant recipients. In addition, the nature of fatigue and factors that may be associated with severity of fatigue after liver transplantation were explored.

Design Cross-sectional study.

Methods Ninety-six patients up to 15 years after liver transplantation were included. Severity of fatigue and nature of fatigue were assessed with the Fatigue Severity Scale (FSS) and the Multidimensional Fatigue Inventory, respectively. Furthermore, age, gender, indication for transplantation, time since transplantation, immunosuppressive medication, self-experienced disability, and health-related quality of life (HRQoL) were assessed as potential associated factors.

Results Sixty-six percent of all patients was fatigued (FSS≥ 4.0) and 44% of all patients was severely fatigued (FSS≥ 5.1). Patients experienced physical fatigue and had reduced activity rather than mental fatigue and reduced motivation. Age, gender, self-experienced disabilities, and HRQoL were correlated with severity of fatigue.

Discussion Results of the study indicate that fatigue is a major problem in patients after liver transplantation, and no indications were found that complaints of fatigue improve over time. Liver transplant recipients experience physical fatigue and reduced activity rather than mental fatigue and reduced motivation. These findings have implications for the development of interventions needed to rehabilitate persons after liver transplantation.

Introduction

Fatigue is common in end-stage liver disease[1-6], and can contribute to the indication for liver transplantation.[7] Particularly in primary biliary cirrhosis (PBC), up to 81% of patients report fatigue to be their most important complaint.[8]

The few studies on fatigue after liver transplantation also report that patients experience fatigue.[6, 9-11] For example, Gross et al.[6] and Belle et al.[11] found that although the intensity of fatigue was reduced after liver transplantation, fatigue remained the most distressing symptom one year after transplantation.

It may be hypothesized that rehabilitation programs can be effective in reducing the complaints of fatigue after liver transplantation. However, besides needing more insight into the severity of the complaints, knowledge on the nature of fatigue after liver transplantation is a prerequisite for the development of interventions to successfully rehabilitate liver transplant recipients. Reports on the nature of fatigue after liver transplantation are scarce. Aadahl et al.[10] reported that liver transplant recipients experience physical fatigue and reduced activity rather than mental fatigue and reduced motivation, and our group found that fatigued liver transplant recipients have a sedentary lifestyle.[12]

The aim of the present study was to assess the severity of fatigue after liver transplantation. In addition, the nature of fatigue and factors that may be associated with severity of fatigue after liver transplantation were explored.

Methods

Subjects

All liver transplant recipients older than 18 years who visited our outpatient clinic between February 2003 and June 2003 and who were able to read Dutch were eligible for the study if they had given written informed consent. Subjects were excluded when they had severe concomitant medical conditions, or were discharged less than 3 weeks before the visit. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center Rotterdam. A total of 96 liver transplant recipients agreed to participate (45 men and 51 women). There were no differences in relevant characteristics between the participants and the liver transplant recipients treated in our clinic who were not asked to participate.

Severity of fatigue

Severity of fatigue was measured by the Fatigue Severity Scale (FSS).[13] The FSS is a self-assessed nine-item questionnaire. The mean score of the nine questions ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Internal consistency (Cronbach's alpha ranging from 0.81 to 0.95), test-retest reliability (intraclass correlation coefficient ranging from 0.82 to 0.86), validity (correlation coefficients between FSS and Visual Analogue Scales ranging from 0.47 to 0.81; correlation coefficients between FSS and health-related quality of life ranging from -0.76 to -0.22) and sensitivity of the FSS (magnitude of change on the FSS ranging from 0.5 to 3.5 points) have been shown in several patient groups, including chronic liver disease.[13-15] In the present study 'severe fatigue' was defined as a score on the FSS of more than 2 standard deviations (SD) above the mean score in healthy individuals (FSS≥ 5.1).[15] 'Fatigue' was defined as a score on the FSS of more than 1 SD above the mean score in healthy individuals (FSS≥ 4.0).

Nature of fatigue

The nature of fatigue was measured by the Multidimensional Fatigue Inventory (MFI-20).[16] The MFI-20 is a self-report instrument consisting of 20 items divided into one general fatigue scale and four different 'nature of fatigue' scales (i.e. physical fatigue,

reduced activity, reduced motivation, and mental fatigue). Each scale consists of four items, with a five-point response format. Subscale scores range from 4 to 20; a higher score indicates more fatigue. Internal consistency (Cronbach's alpha ranging from 0.53 to 0.93), test-retest reliability (Pearson correlation coefficients ranging from 0.74 to 0.87), validity (correlation coefficients between MFI-20 and Visual Analogue Scales, health-related quality of life, activity of daily living, anxiety, and depression ranging from 0.23 to 0.84), and discriminative ability of the MFI-20 have been shown in several groups, including chronic liver disease.[16-18]

Factors potentially associated with severity of fatigue after liver transplantation

Self-experienced disability

Disability level was assessed with the self-assessment version of the Sickness Impact Profile-68 (SIP-68). The SIP-68 describes the impact of illness on daily functioning and behaviour, and consists of six scales covering three broad dimensions, i.e. physical, physiological, and social daily functioning.[19, 20] Internal consistency (Cronbach's alpha ranging from 0.49 to 0.94), test-retest reliability (intraclass correlation coefficient ranging from 0.90 to 0.97 and Pearson correlation coefficient ranging from 0.76 to 0.90), and validity (correlation coefficients between SIP-68 and health-related quality of life ranging from 0.41 to 0.71) of the SIP-68 have been shown.[18,19] Patients were asked to mark the statements that apply to their perceived health. The total score ranges from 0 to 68, with higher scores indicating a higher disability level. The SIP-68 is widely used in research in liver transplant recipients.[21-23]

Health-related quality of life

Health-related quality of life (HRQoL) was assessed with a validated Dutch version of the Medical Outcomes Study Short Form-36 (SF-36)[24], the RAND-36.[25] The SF-36 is a self-administered questionnaire used internationally to measure health status with respect to different dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, pain, mental health, vitality, and general health perception.[26] Additionally, one single item assesses change in perceived health during the last 12 months. Internal consistency (Cronbach's

alpha ranging from 0.66 to 0.93) and test-retest reliability (Pearson correlation coefficient ranging from 0.63 to 0.90) have been shown.[18, 26] Furthermore, statistically significant differences in SF-36 scores have been observed as a function of age, gender, and the prevalence of chronic health conditions.[26] All raw scales are linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of HRQoL.

Furthermore, age, gender, indication for liver transplantation (acute or chronic liver failure), time since liver transplantation, and use of immunosuppressive medication were assessed from the medical record as potential associated factors of severity of fatigue after liver transplantation.

Protocol

Participants received the questionnaires after they were instructed about the procedure by a research nurse. Additional written instructions were attached to the questionnaires.

Statistical analysis

Statistical analysis was performed using SPSS 10.1 for Windows. Data were presented as mean with SD unless otherwise indicated. Using the Pearson correlation coefficient (r) and partial correlation analysis, we investigated relationships between parameters. Comparisons between subgroups were made using the independent t-test for unpaired samples and the Chi-square test. To compare the different dimensions of the MFI-20, analysis of repeated measurements was performed, followed by paired t-tests. A probability value $p \leq .05$ determined statistical significance.

Results

Table 1 presents the characteristics of the study sample. The indication for liver transplantation was relatively more often acute in women than in men ($p=.01$). None of the participants used medication to treat fatigue or used anti-depressive medication.

Table 1. Characteristics of the study population (n=96)

	Total group (n=96)			Men (n=45)			Women (n=51)			
	n	Mean	SD	n	Mean	SD	n	Mean	SD	p-value
Age (yrs)		51.8	12.7		52.6	12.5		51.1	12.9	.55
Indication [a]										
Acute	17			3			14			.01†
Chronic	79			42			37			
Time since transplantation (months) [b]		54	45.4		49	36		58	52	.30
Immunosuppressive agent (number)										
1	43			23			20			
2	37			17			20			.31
3	16			5			11			

None of the participants used medication to treat fatigue or used anti-depressive medication

[a] Acute primary disease: hepatitis B cirrhosis (n=1), hepatitis e.c.i. (n=1), hepatitis B + HIV (n=1), intoxication (n=3), 'M.wilson'(n=1), unknown (n=10); Chronic primary disease: cholestatic (n=23), viral (n=24), alcoholic (n=6), miscellaneous (n=26)

[b] Time since transplantation ranged from 52 days to 5623 days (15.4 years)

* P-value for the difference between men and women

† significantly different (p≤ .01) between men and women

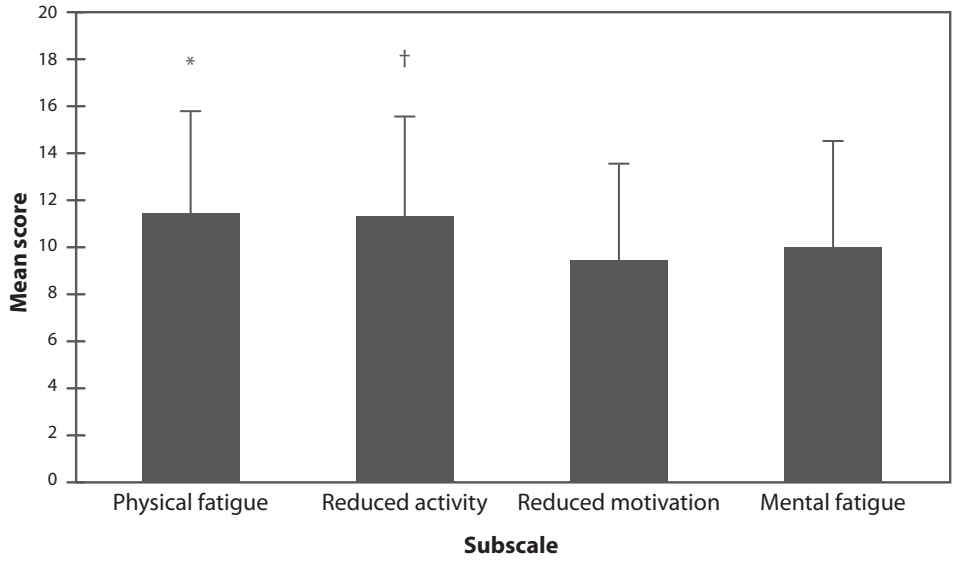
Severity of fatigue

Mean (SD) score on the FSS was 4.66 (1.56), ranging from 1.00 to 7.00. According to our criteria, 66% of all patients was fatigued (FSS≥ 4.0) and 44% of all patients was severely fatigued (FSS≥ 5.1).

Nature of fatigue

Figure 1 shows the mean (SD) scores on the different subscales of the MFI-20. There was a significant difference in scores between the different subscales (p<.001), with the scores on the physical fatigue subscale and the reduced activity subscale being significantly higher (indicating more fatigue) than the scores on the reduced motivation subscale and the mental fatigue subscale.

Figure 1. Nature of fatigue as assessed with the Multidimensional Fatigue Inventory



A higher score indicates more fatigue
* significantly higher than the reduced motivation subscale (p<.001) and mental fatigue subscale (p<.05)
† significantly higher than the reduced motivation subscale (p<.001) and mental fatigue subscale (p<.01)

Factors potentially associated with severity of fatigue

Table 2 shows the results on self-experienced disability and HRQoL, and Table 3 gives the correlation coefficients between potential associated factors and the severity of fatigue. Gender and age were significantly correlated with the score on the FSS (p=.01 and p=.05, respectively), indicating that women were more severely fatigued than men, and that older recipients were more severely fatigued than younger recipients (Table 3). To adjust for the influence of these non-disease related factors, relationships between the other potential associated factors and the score on the FSS were also assessed with partial correlation analysis, adjusting for gender and age (Table 3). Without adjustment for gender and age, time since transplantation, self-experienced disabilities, and HRQoL were significantly correlated with the severity of fatigue. However, after adjusting for gender and age, the relationship between time since

Table 2. Mean (SD) scores on self-experienced disability as assessed with the Sickness Impact Profile and health-related quality of life as assessed with the RAND-36

	Mean	SD
Self-experienced disability	9.4	9.7
Health-related quality of life		
Physical functioning	67.8	24.1
Social functioning	78.9	23.6
Role physical	53.4	44.2
Role emotional	73.0	39.9
Mental health	71.7	19.3
Vitality	54.5	21.5
Bodily pain	72.7	28.5
General health perception	48.4	21.7
Health transition	64.3	30.1

transplantation and severity of fatigue was no longer significant. No relations were found between indication for liver transplantation and immunosuppressive medication on the one hand and severity of fatigue on the other.

Discussion

This is the first study to provide information on both the severity and nature of fatigue after liver transplantation, and on factors associated with the severity of fatigue. Since our study population was a relatively large random sample, consisting of almost 50% of all liver transplant recipients that are treated in our hospital, we believe that our conclusions can be generalised to the population of liver transplant recipients.

Our study may, however, have some limitations. First, shortly after transplantation subjects may be in an almost euphoric mood[9], which may lead to an underestimation of the severity of fatigue. Later on, subjects may be disappointed by delayed complications of the transplantation and medication or sustained complaints, which may lead to an overestimation of the severity of fatigue (response shift).[27] Secondly, our study sample was heterogeneous with respect to time after transplantation and because of the cross-sectional design, results on the course of fatigue since transplantation have to be interpreted with caution. Finally, the primary aim of our

Table 3. Pearson correlation coefficients and partial correlation coefficients, adjusted for gender and age, for the relationships between potential associated factors and severity of fatigue

	Pearson analysis	p-value	Partial analysis	p-value
Gender	.26	.01†		
Age	.20	.05*		
Time since transplantation	.26	.01†	.16	.13
Indication (acute or chronic)	-.16	.12	-.12	.26
Immunosuppressive medication	.11	.31	.07	.52
Self-experienced disability (SIP-68)	.58	.00†	.59	.00†
Health-related quality of life (RAND-36)				
Physical functioning	-.47	.00†	-.41	.00†
Social functioning	-.53	.00†	-.53	.00†
Role physical	-.60	.00†	-.55	.00†
Role emotional	-.44	.00†	-.45	.00†
Mental health	-.50	.00†	-.50	.00†
Vitality	-.64	.00†	-.61	.00†
Bodily pain	-.45	.00†	-.43	.00†
General health perception	-.59	.00†	-.54	.00†
Health transition	-.36	.00†	-.29	.01†

* significant correlation (p≤ .05) with severity of fatigue
† significant correlation (p≤ .01) with severity of fatigue

study was to assess severity of fatigue in liver transplant recipients. Therefore, we by no means imply that our list of factors that may be associated with fatigue in liver transplant recipients is complete.

The present study shows that fatigue is a major problem in patients after liver transplantation, which is in agreement with previous studies.[6, 9-11] Of our liver transplant recipients, 66% experienced fatigue and in 44% of the participants these complaints were severe. Furthermore, we found no association between time since transplantation and severity of fatigue (adjusted for gender and age), indicating that complaints do not change over time. This is in contrast with the findings of Aadahl et al.[10], who found that patients who had undergone liver transplantation 4 to 5 years previously were less fatigued than patients who had undergone liver transplantation more recently. However, it should be realized that response shift may have influenced

our results and, furthermore, a cross-sectional study design is not optimal to assess the course of fatigue since transplantation.

Although study groups cannot properly be compared, the severity of complaints of fatigue after liver transplantation as found in the present study is even higher than the severity of complaints (also assessed with the FSS) in patients with PBC.[2] This is remarkable, because fatigue can be one of the indications for transplantation in liver disease[7], and is expected to decrease after transplantation.

We hypothesized that fatigue after liver transplantation is caused by many factors, both physical and psychological. However, similar to the findings of Aadahl et al.[10], our liver transplant recipients experienced physical fatigue and reduced activity rather than mental fatigue and reduced motivation. In addition, a previous study by our group using an activity monitor, demonstrated that fatigued liver transplant recipients have a sedentary lifestyle.[12] These findings imply that fatigue after liver transplantation might be reduced with rehabilitation programs focusing on improving activity patterns and physical fitness. However, to fully understand the nature of fatigue in liver transplant recipients, more research is needed. Currently a project is being performed at our department, focusing on relationships between severity of fatigue on the one hand and depression, anxiety, sleep quality, complications after transplantation, and physical fitness on the other in liver transplant recipients.

Gender, age, self-experienced disabilities, and HRQoL were associated with the severity of fatigue. The relationships between severity of fatigue on the one hand, and gender and age on the other were weak; self-experienced disabilities and HRQoL showed moderate relationships with severity of fatigue. We have no explanation for the finding that female subjects were more fatigued than male subjects. The finding that HRQoL was associated with severity of fatigue is in agreement with the study of Kleinman et al.[14] who found that all HRQoL dimensions were significantly correlated with fatigue ($r=-0.49$ to $r=-0.76$) in patients with chronic liver disease.

Contrary to our expectations, the indication for liver transplantation was not associated with severity of fatigue. Because a period of deconditioning has preceded the transplantation, we expected patients with a chronic indication for liver transplantation to be more fatigued after transplantation than patients with an acute indication. However, on the other hand, patients with a chronic disease prior to transplantation may experience post-transplantation complications, such as fatigue, less negatively than patients who only had a short period of disease before transplantation. This may counterbalance the possible effect of deconditioning on

severity of fatigue in liver transplant recipients. Furthermore, we also expected that patients using several immunosuppressive agents would be more fatigued than patients who have single immunosuppressive medication, because of more side-effects such as myopathy and poor exercise performance.[28, 29] This was not confirmed by the results of the present study.

Conclusion

The study indicates that fatigue is a major problem in patients after liver transplantation. Almost half of the liver transplant recipients was severely fatigued, and no indications were found that complaints of fatigue improve over time. The severity of fatigue was associated with gender, age, self-experienced disabilities, and HRQoL. No relationships were found between the severity of fatigue on the one hand and indication for liver transplantation or immunosuppressive medication on the other. Liver transplant recipients experience physical fatigue and reduced activity rather than mental fatigue and reduced motivation. These findings imply that rehabilitation programs, focusing on improving activity patterns and physical fitness, may reduce complaints of fatigue after liver transplantation.

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Chapter 3

Persistent fatigue in liver transplant recipients: a two-year follow-up study

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Abstract

Objective Fatigue after liver transplantation (LTx) is a major problem that is associated with lower daily functioning and health-related quality of life (HRQoL). This study aimed to assess changes over time in fatigue following LTx. We also examined daily functioning and HRQoL changes over time, and their associations with changes in fatigue severity. We determined whether sleep quality, anxiety, and depression were associated with fatigue.

Design Longitudinal study.

Methods We identified 70 LTx recipients who had previously participated in a cross-sectional study, and reassessed them at two years to determine changes in level of fatigue, daily functioning, and HRQoL. We also assessed sleep quality, anxiety, and depression at two years.

Results Level of fatigue and level of daily functioning were unchanged at follow-up. HRQoL domains remained stable or worsened. Individual changes in fatigue were associated with changes over time in daily functioning and most HRQoL domains ($r=.25$ to $r=.41$, $p< .05$). Sleep quality, anxiety, and depression were associated with fatigue severity ($r=.35$ to $r=.60$, $p< .05$).

Discussion This longitudinal study shows that fatigue is a chronic problem after LTx, and that daily functioning and HRQoL do not improve over time. This study supports the need for intervention programs to address fatigue after LTx.

Introduction

Over the past few decades, liver transplantation (LTx) has been associated with improved one- and five-year survival rates, and fewer rejection episodes.[1] However, fatigue remains one of the most distressing symptoms after LTx.[2, 3] Fatigued LTx recipients report lower levels of health-related daily functioning and health-related quality of life (HRQoL) compared to non-fatigued LTx recipients.[4] Although the cause of fatigue after LTx is often unclear, previous studies demonstrate associations with age, sex, level of physical activity, and cardiorespiratory fitness.[4-6] It may be hypothesized that poor sleep quality, anxiety, and depression, which are associated with fatigue in chronic fatigue patients[7, 8], are also associated with fatigue after LTx.

Conflicting data exist regarding changes over time in fatigue after LTx. In a previous study, we found that 66% of the studied LTx recipients (time since LTx 4.5 ± 3.8 years) reported fatigue, but there was no relationship between time after LTx and fatigue, implying that fatigue does not change over time.[4] In contrast, Aadahl et al. found that fatigue was less severe in patients who had undergone LTx four to five years previously when compared with patients who had undergone LTx more recently.[9] However, both studies were limited by a cross-sectional design. To our knowledge, no longitudinal studies on the course of fatigue after LTx have been published.

The aim of this longitudinal study was threefold. First, we aimed to assess whether fatigue changes over time after LTx. Secondly, we aimed to determine if daily functioning and HRQoL changes over time, and if these changes are associated with changes in severity of fatigue over time. Lastly, we aimed to determine whether sleep quality, anxiety, and depression are associated with fatigue after LTx.

Methods

Subjects

We identified LTx recipients who had participated in a previous cross-sectional study[4], and reassessed them two years later. Eligible subjects were aged 18 or older and had sufficient knowledge of the Dutch language. Patients with severe co-morbid medical conditions (e.g. cancer, stroke, severe musculoskeletal disorders, psychological disorders) were excluded.

Protocol

The research team contacted eligible patients by telephone to describe the research and obtain informed consent. Interested patients were sent five questionnaires by postal mail. Three of the questionnaires were identical to those completed at the baseline cross-sectional survey two years earlier. These three questionnaires addressed severity of fatigue, daily functioning and HRQoL. We also asked patients to complete two additional questionnaires: one about sleep quality, and one about anxiety and depression. Written instructions were provided with each questionnaire. Medical records were reviewed to obtain data on patient age, sex, cause of liver disease, urgency status at time of LTx, time of onset to listing to transplantation, liver function, kidney function, number of rejections, presence of cancer, infections, hypertension, haemoglobin levels, body weight, and type and number of immunosuppressive agents.

Instruments

Severity of fatigue

We assessed severity of fatigue using the validated Dutch version of the Fatigue Severity Scale (FSS).[10] The FSS is a nine-question, self-administered questionnaire with answers ranging from 1 ('strongly disagree') to 7 ('strongly agree'). For each patient, the mean question score ranged from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Internal consistency, reliability, validity and sensitivity of the FSS have been shown for patients with chronic liver disease.[10-12] As in our previous study[4], we classified patients as 'severely fatigued' for FSS scores more than or equal to two

standard deviations (SD) above the mean score for healthy individuals (FSS ≥ 5.1). Patients were classified as 'fatigued' for FSS scores more than or equal to 1 SD above the mean score for healthy individuals (4.0 ≤ FSS < 5.1). Improvement or worsening in fatigue was defined as changes in FSS score of more than 1 point at follow-up.[13]

Health-related daily functioning

We assessed health-related daily functioning using the self-assessment version of the Sickness Impact Profile-68 (SIP-68). The SIP-68 assesses the impact of illness on daily functioning and behaviour. It includes six scales that cover three broad categories of functioning: physical, psychological, and social.[14, 15] The total score ranges from 0 to 68, with higher scores indicating a lower level of daily functioning. The SIP-68 is widely used in studies of LTx recipients.[4, 16-18]

Health-related quality of life

We assessed HRQoL using the validated Dutch version of the Medical Outcomes Study Short Form-36, the RAND-36 Health Survey (RAND-36).[19] The RAND-36 is a self-administered questionnaire used internationally to measure health status with respect to physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, pain, mental health, vitality, general health perception, and perceived change in health during the previous 12 months.[20] We converted all raw scores to a 100-point scale, with higher scores indicating higher levels of HRQoL.

Anxiety and depression

We assessed anxiety and depression using the Hospital Anxiety and Depression Scale (HADS). [21-23] This 14-item validated, self-administered questionnaire measures symptoms of anxiety (7 items) and depression (7 items) occurring during the previous week. For both the anxiety (HADS-A) and depression (HADS-D) subscales, scores ranged from 0 to 21; higher scores indicate a higher degree of anxiety or depression. A score of eight or more on either subscale indicates possible anxiety or depression.[23]

Sleep quality

We assessed sleep quality using the Pittsburgh Sleep Quality Index (PSQI).[24] The PSQI is a validated, self-rated questionnaire that assesses sleep quality and disturbances for the preceding month. The PSQI consists of 19 self-rated questions and 5 questions rated by a bed partner or roommate (the latter five questions were not used in the analyses). We analyzed the 19 self-rated questions, grouped into seven component scores, each weighted equally on a 0 to 3 point scale. The components are: subjective sleep quality, sleep latency, sleep duration, sleep efficiency (i.e. ratio of total sleep time to time in bed), sleep disturbances (e.g. insomnia, nightmares, sleep apnea), use of sleep-inducing drugs, and daytime functioning. The seven component scores were then summed to yield global PSQI scores, which may range from 0 to 21. A global PSQI score greater than 5 indicates poor sleep quality.

Statistical analysis

We used SPSS 10.1 for Windows (SPSS Inc., Chicago, IL, USA) for statistical analyses. We present data as mean with SD unless otherwise indicated. Changes in mean severity of fatigue, daily functioning, and HRQoL over the two-year period were tested with a paired t-test. We used a McNemar-Bowker test of symmetry to determine differences in individual classifications of fatigue (no fatigue, fatigue, and severe fatigue) between baseline and follow-up. Using the Pearson correlation coefficient (r), we investigated the relationship between changes over time in severity of fatigue, and changes over time in daily functioning and HRQoL. To assess the relationship between severity of fatigue and sleep quality, anxiety, and depression, we used partial correlation analysis, controlling for sex and age. A p-value ≤ .05 was deemed statistically significant.

The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center Rotterdam. Written informed consent was obtained from all subjects.

Results

Of 96 patients eligible to participate from the previous study[4], 70 patients (73%) gave informed consent to participate (39 women and 31 men). Eleven patients did not respond to telephone calls or information letters; three patients did not wish to participate for undisclosed reasons; six patients were excluded for severe co-morbidity (cancer (1), stroke (1), severe loss of leg function (1), severe hip problems (2), psychological disorder (1)); five had died; one had emigrated. Patients' characteristics are presented in Table 1. Reported co-morbidities of the patients that were included in the study were diabetes mellitus (21%), hypertension (14%), and Crohn's disease (13%).

There were no significant differences in age and sex between participants and nonparticipants. However, mean fatigue score at baseline was significantly higher in non-participants (5.22 ± 1.21) compared to participants (4.45 ± 1.63) (p= .01).

Time course of fatigue

Mean severity of fatigue at the two-year follow-up was unchanged from baseline (p= .89; Table 2). For individual classifications, the proportion of patients reporting no fatigue (FSS < 4), fatigue (4.0 ≤ FSS < 5.1), and severe fatigue (FSS ≥ 5.1) was at baseline 40%, 20%, and 40%, respectively. At follow-up, levels were reported as 37%, 20%, and 43%, respectively. Individual classifications of fatigue did not change significantly between baseline and follow-up (p= .52). Most patients (71.4%) that were severely fatigued at baseline were also severely fatigued at follow-up. Half of patients reporting fatigue at baseline reported severe fatigue at follow-up; 71.4% of patients reporting no fatigue at baseline reported no fatigue at follow-up (Table 3). Post-hoc analysis revealed that individual changes in fatigue score of more than 1 point were not associated with major events (rejection, de novo cancer, infection, recurrence of disease) or changes in clinical factors (immunosuppressive agents, liver function, kidney function, hemoglobin, body weight) during the studied two years (chi-square test).

Time course of daily functioning and HRQoL

Daily functioning and most HRQoL domains remained unchanged from baseline to follow-up (Table 2). However, the HRQoL domains 'social functioning' and 'change in health' demonstrated significantly lower scores compared to baseline (p≤ .01).

Table 1. Patient characteristics (n=70)

Age (years)	52.5 ± 12.3
Sex (%)	
Women	56%
Men	44%
Time since transplantation (years)	6.7 ± 3.8 years
Pre-transplant diagnoses (%)	
Chronic	80%
Acute	20%
Liver disease etiology (%)	
Cholestatic liver disease	27%
Viral cirrhosis	24%
Alcohol-related cirrhosis	9%
Hepatocellular carcinoma	6%
Other	7%
Cryptogenic cirrhosis	27%
Urgency status (%)	
High Urgency [a]	24%
Urgency [b]	7%
T [c]	37%
T2 [d]	4%
T3 [e]	20%
T4 [f]	1%
Unknown [g]	6%
Time of onset to listing to transplantation (months)	4.2 ± 4.5 months

Cholestatic liver disease: PSC (n=9), PBC (n=7), SBC (n=2), Byler disease (n=1)
Viral cirrhosis: hepatitis B (n=9), hepatitis B+C (n=6), hepatitis C (n=2)
Hepatocellular carcinoma: benign liver tumors (n=3), malignant liver tumors (n=1)
Other: auto-immune hepatitis (n=4), M.Wilson (n=1)

[a] High Urgency (n=17)
[b] Urgency (n=5): classification before October 2000
[c] T, Transplantable (n=26): classification before October 2000
[d] T2, Chronic disease acute deterioration (n=3): classification since October 2000
[e] T3, Chronic disease complications (n=14): classification since October 2000
[f] T4, Chronic disease no complications (n=1): classification since October 2000
[g] Unknown (n=4): not transplanted at our hospital

Table 2. Mean (SD) severity of fatigue, daily functioning, and health-related quality of life at baseline and two years

	Baseline (N=70)	2-year follow-up (N=70)	p-value
Severity of fatigue (FSS)	4.45 ± 1.63	4.47 ± 1.79	.89
Daily functioning (SIP-68)	9.4 ± 9.7	8.6 ± 8.4	.66
Health-related quality of life (RAND-36)			
Physical functioning	67.8 ± 24.1	69.0 ± 25.9	.33
Social functioning	78.9 ± 23.6	70.6 ± 25.8	.01†
Role functioning physical	53.4 ± 44.2	52.5 ± 42.0	.90
Role functioning emotional	73.0 ± 39.9	71.0 ± 40.1	.23
Mental health	71.7 ± 19.3	74.8 ± 16.3	.70
Vitality	54.5 ± 21.5	56.0 ± 22.0	.83
Bodily pain	72.7 ± 28.5	73.7 ± 29.5	.64
General health perception	48.4 ± 21.7	52.3 ± 21.1	.40
Change in health	64.3 ± 30.1	54.0 ± 25.0	≤.01†

FSS: Fatigue Severity Scale. Higher scores indicate a higher level of fatigue
SIP-68: Sickness Impact Profile 68. Higher scores indicate a lower level of daily functioning
RAND-36: Short Form Health Survey-36. Higher scores indicate higher levels of health-related quality of life
† Significant difference (p≤ .01) between baseline and two-year follow-up

Table 3. Distribution of fatigue at follow-up, by fatigue level at baseline

	n	Percentage
Severe fatigue at baseline (FSS score ≥ 5.1)	**28**	**40.0%**
severe fatigue at follow-up	20	71.4%
fatigue at follow-up	4	14.3%
no fatigue at follow-up	4	14.3%
Fatigue at baseline (4.0 ≤ FSS score < 5.1)	**14**	**20.0%**
severe fatigue at follow-up	7	50.0%
fatigue at follow-up	5	35.7%
no fatigue at follow-up	2	14.3%
No fatigue at baseline (FSS < 4.0)	**28**	**40.0%**
severe fatigue at follow-up	3	10.7%
fatigue at follow-up	5	17.9%
no fatigue at follow-up	20	71.4%

FSS: Fatigue Severity Scale

Correlations between changes over time in fatigue, and changes over time in daily functioning and HRQoL

A reduction in severity of fatigue was associated with improvement in daily functioning and in the HRQoL domains of 'physical functioning', 'social functioning', 'role functioning physical', 'mental health', 'vitality', and 'change in health' ($p < .05$; Table 4).

Correlations between fatigue and anxiety, depression and sleep quality

Anxiety, depression, and sleep quality were significantly associated with severity of fatigue when controlled for age and sex ($r = .30$ to $r = .60$, $p < .05$; Table 5). HADS-D and HADS-A scores were 5.1 ± 4.6 and 4.8 ± 4.2. The proportion of patients with a possible diagnosis of anxiety or depression (HADS ≥ 8) was 27% and 26%. Mean PSQI score was 6.6 ± 4.2. A total of 51% of the patients reported poor sleep quality (PSQI > 5).

Table 4. Correlation between changes over time in severity of fatigue, and changes over time in daily functioning and health-related quality of life

	Change in severity of fatigue (FSS)	
	Pearson analysis	**p-value**
Change in daily functioning (SIP-68)	.37	≤.01†
Change in health-related quality of life (RAND-36)		
Physical functioning	-.41	.00†
Social functioning	-.25	.04*
Role functioning physical	-.31	.01†
Role functioning emotional	-.03	.82
Mental health	-.30	.01†
Vitality	-.32	.01†
Bodily pain	-.09	.48
General health perception	-.22	.07
Change in health	-.27	.02*

FSS: Fatigue Severity Scale. Higher scores indicate a higher level of fatigue
SIP-68: Sickness Impact Profile 68. Higher scores indicate a lower level of daily functioning
RAND-36: Short Form-36. Higher scores indicate higher levels of health-related quality of life
* Significant correlation ($p \leq .05$) with change over time in severity of fatigue
† Significant correlation ($p \leq .01$) with change over time in severity of fatigue

Table 5. Correlation between fatigue severity and anxiety, depression, and sleep quality, controlled for age and sex

	Severity of fatigue (FSS)			
	Pearson analysis	**p-value**	**Partial analysis**	**p-value**
Anxiety (HADS-A)	.56	≤.01†	.54	≤.01†
Depression (HADS-D)	.60	≤.01†	.60	≤.01†
Sleep quality (PSQI) [a]	.35	≤.01†	.30	≤.01†

FSS: Fatigue Severity Scale. Higher scores indicate a higher level of fatigue
HADS: Hospital Anxiety and Depression Scale. Higher scores indicate a higher degree of anxiety or depression
PSQI: Pittsburgh Sleep Quality Index. Higher scores indicate poorer sleep quality
[a] **Note:** N=69 because of 1 missing questionnaire.
† Significant correlation (p≤ .01) with severity of fatigue

Discussion

To our knowledge this is the first longitudinal study of time course of fatigue following LTx. At baseline, 20% of patients reported fatigue and 40% reported severe fatigue according to FSS classification. Two years later there were no significant changes, suggesting that fatigue is a chronic problem following LTx. Individual changes in fatigue score of more than 1 point were not associated with major events, such as rejection, or changes in clinical factors, such as immunosuppressive agents, during the studied period. Previous studies in LTx recipients and in patients with multiple sclerosis also showed that the use of immunosuppressive agents was not associated with the level of fatigue.[4, 25] However, studies concerning this topic are scarce and contradictory.[26]

This persistence of fatigue is consistent with results from our previous cross-sectional study[4], which demonstrated no association between time since LTx and severity of fatigue. However, the findings do contrast with those of Aadahl et al.[9], who found that fatigue was less severe in patients who had undergone LTx four to five years previously when compared with patients who had undergone LTx more recently. The difference in results may be due to differences in sampling groups. Aadahl et al. used a cross-sectional design comparing fatigue in two different patient samples: patients one to three years since LTx, and patients four to five years since LTx, whereas we studied relationships within one patient sample. Except for studies

comparing pre- and post-transplant fatigue[27-30], no longitudinal studies have assessed the course of fatigue following LTx or other organ transplantations (e.g. heart, kidney, lung).

Dew et al. reported that quality of life after transplantation (bone marrow, kidney, pancreas, heart, lung, liver) remained stable or improved during the first one to seven years post transplantation.[31] Our study demonstrated no change in most quality-of-life domains and daily functioning over time. However, subjects indicated a clinically significant decline (i.e. a difference of five or more points[32]) in two HRQoL domains; they reported poorer social functioning and more severe deterioration in health longer after LTx. The decrease in daily functioning and HRQoL domains in LTx recipients who became more fatigued over time is consistent with our previous cross-sectional study.[4]

Prevalence of anxiety and depression following LTx has been extensively studied and yields conflicting results.[9, 33-35] The mean HADS anxiety score of 5.1 in this study was comparable to the mean anxiety score for the referent Dutch population (i.e. HADS-A score 5.1), but the mean HADS depression score of 4.8 was higher compared to the referent Dutch population (i.e. HADS-D score 3.4).[22] Authors reporting a high prevalence of anxiety or depression in LTx recipients attribute this finding to patients' experience of a major life event or because they have adopted the 'sick role' and have difficulty readjusting to a healthy role.[33, 34] However, other authors suggest that survival from a potentially lethal disease changes internal standards and values as well as the meaning of anxiety, depression, and fatigue (response shift).[9, 35, 36]

The prevalence of poor sleep quality in the present study is higher compared to the general population. In the general population, 15% to 35% of adults report frequent sleep quality disturbance.[24] Previously reported rates of sleep disturbances after LTx range from 14% to 45%[37-40], whereas 51% of our study patients reported sleep disturbance.

The present study indicates that sleep quality, anxiety, and depression are associated with fatigue. Because of the cross-sectional design, it is unknown whether these relationships are causal. These factors often co-exist with fatigue[7, 8], and should therefore be targeted by interventions designed to reduce fatigue in LTx recipients. Swain et al. have suggested that depression treatments may also be useful in treating fatigue associated with chronic disease.[7] Previous studies indicate that level of everyday physical activity and cardiorespiratory fitness may also be associated with the severity of fatigue after LTx.[5, 6] Therefore fatigue-reduction strategies for LTx recipients may need to additionally target physical activity and cardiorespiratory fitness.

A limitation of our study is that the reported severity of fatigue may be an underestimation due to selection bias. The patients that did not participate in the follow-up measurement were more fatigued at baseline compared to those who participated in both measurements. This may make the study results less generalizable to the liver transplant recipient population.

In conclusion, results of the present study indicate that fatigue is a chronic problem for LTx recipients, and that daily functioning and HRQoL do not improve during the post-LTx period. Although there were no changes over time at group level, individual changes over time in fatigue were associated with changes over time in daily functioning and in most HRQoL domains. Results of this study support the need for specific intervention programs to address fatigue in LTx recipients.

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Chapter 4

Physical fitness, fatigue and quality of life after liver transplantation

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Abstract

Objective Fatigue is often experienced after liver transplantation. The aims of this cross-sectional study were to assess physical fitness (aerobic capacity, muscle strength, body composition) in liver transplant recipients, and to explore whether physical fitness is related to severity of fatigue. In addition, we explored the relationship between physical fitness and health-related quality of life.

Design Cross-sectional study.

Methods Included were 18 patients 1-5 years after transplantation (aged 48.0 ± 11.8 years) with varying severity of fatigue. Peak oxygen uptake during cycle ergometry, 6-minute walk distance, isokinetic muscle strength of the knee extensors, body mass index, waist circumference, skinfold thickness, severity of fatigue, and health-related quality of life were measured.

Results Aerobic capacity in the liver transplant recipients was on average 16 to 34% lower than normative values ($p \leq .05$). Furthermore, the prevalence of obesity seemed to be higher than in the general population (17% versus 10%). We found no deficit in muscle strength. Aerobic capacity was the only fitness component that was related with severity of fatigue ($r = -.61$ to $r = -.50$, $p \leq .05$). Particularly aerobic capacity was related with several aspects of health-related quality of life ($r = .48$ to $r = .70$, $p \leq .05$).

Discussion Results of our study imply that aerobic capacity and body composition are impaired in liver transplant recipients, and that fitness is related with severity of fatigue (only aerobic capacity) and quality of life (particularly aerobic capacity) in this group. These findings have implications for the development of rehabilitation programs for liver transplant recipients.

Introduction

Liver transplantation (LTx) is the only definitive treatment for end-stage liver disease. Since 1988, patient survival and liver function after LTx have improved markedly, due to improved technical expertise, better selection of patients, improved post-LTx management of complications, and improved immunosuppressive therapy.[1] In Europe, LTx has achieved a 1-year survival rate of 82%.[2]

Although studies have reported that quality of life improves after LTx, limitations in daily function still remain.[3, 4] Amongst these limitations, liver transplant recipients often experience fatigue.[5-8] Gross et al.[3] and Belle et al.[6] reported that, although the intensity of fatigue was reduced after LTx, fatigue remained the most distressing symptom one year after surgery. Leyendecker et al.[7] found that 9 months after LTx, complaints of fatigue were more severe in the LTx group than in the general population. In a previous study, we found severe fatigue in 44% of patients up to 15 years after LTx, and these complaints did not decrease over time.[8]

Rehabilitation programs might be effective in reducing severity of fatigue after LTx, but, to develop appropriate programs, knowledge on the factors associated with fatigue after LTx is necessary. However, data on these factors are scarce. Aadahl et al.[5] and van den Berg-Emons et al.[8] suggested that the fatigue experienced by liver transplant recipients is primarily physical, rather than psychological. Furthermore, van den Berg-Emons et al.[9] found that severe complaints of fatigue in liver transplant recipients are associated with low levels of everyday physical activity. A hypoactive lifestyle may lead to a negative spiral: hypoactivity leading to a reduction in physical fitness and deterioration of complaints of fatigue, leading to further hypoactivity.

Few studies have investigated the physical fitness of liver transplant recipients, but the limited data available suggest a reduced physical fitness after LTx.[10-12] Stephenson et al.[11] found a 40-60% lower maximal oxygen uptake than predicted in liver transplant recipients. Beyer et al.[10] reported that, although the aerobic capacity and muscle strength in liver transplant recipients improved after a supervised exercise program during the post-operative year, maximal oxygen uptake and muscle strength remained 10-20% lower compared to healthy gender and age-matched individuals. Also in pediatric liver transplant recipients, deficits in aerobic capacity and abdominal muscle strength have been reported.[12]

It may be hypothesized that deficits in physical fitness in liver transplant recipients are associated with complaints of fatigue. Furthermore, deficits in physical fitness may

lead to impaired health-related quality of life (HRQoL). However, to our knowledge, no studies are available on the relationships between these parameters in liver transplant recipients.

Because of the scarcity of studies on physical fitness and related parameters in liver transplant recipients, the present study assessed physical fitness (aerobic capacity, muscle strength, and body composition) in liver transplant recipients, and explored whether physical fitness is related to severity of fatigue in this group. The relationship between physical fitness and HRQoL was also explored.

Patients and Methods

Patients

To obtain a representative sample of liver transplant recipients with respect to fatigue, we recruited liver transplant recipients with varying severity of fatigue, according to the distribution of severity of fatigue as found in our previous study in 96 liver transplant recipients.[8] Severity of fatigue in this previous study ranged from 'no signs of fatigue' to 'most disabling fatigue', and was assessed with the Fatigue Severity Scale of Krupp et al.[13] (see below). Inclusion criteria for the present study were: LTx between 1 to 5 years ago, sufficient knowledge of the Dutch language, and age between 18 and 65 years. Exclusion criteria were: multiorgan transplant recipients, severe comorbidity, and contra-indication for a progressive maximal cycle ergometer test. Of the original sample of 96 patients in the previous study[8], 4 patients had died, 1 patient had emigrated, 53 patients were transplanted more than 5 years previously, and 10 patients were not eligible because of contra-indications for a maximal cycle ergometer test. Of the 28 eligible patients, 18 patients (64%) agreed to participate. There were no significant differences in relevant characteristics between the patients who decided to participate and the non-participants. The study was approved by the Medical Ethics Committee of the Erasmus University Medical Center. Written informed consent was obtained from all subjects. Table 1 shows the characteristics of the study group

Table 1. Characteristics of the study group (n=18)

Age (years)	48.0 ± 11.8
Gender	
Male	11
Female	7
Primary disease (n) [a]	
Chronic	17
Acute	1
Time since transplantation (years)	3.3 ± 1.1
Immunosuppressive agents [b]	
1	16
2	1
3	1

Results are presented as mean ± SD or numbers

[a] Chronic primary disease: cholestatic (n=6), viral (n=6), miscellaneous (n=5);
Acute primary disease: intoxication (n=1)

[b] Immunosuppressive agents:
1 agent, cyclosporine or tacrolimus;
2 agents, prednisone with tacrolimus;
3 agents, prednisone with tacrolimus and azathioprine

Measurements

Physical fitness: Aerobic capacity

Aerobic capacity was measured with a progressive maximal aerobic test on a cycle ergometer (ER800, Jaeger Toennies, Breda, The Netherlands). The test was preceded by a 1-minute warm-up period (20 Watt). The test started at 20 Watt, and resistance was increased every minute by 15 or 20 Watt, depending on the ability of the patients. Individual protocols were constructed such that the total exercise time ranged from 8 to 12 minutes. The pedal rate was 60 rpm, and strong verbal encouragement was given during the test. The test was terminated when the subject voluntarily stopped due to exhaustion, or when the patient was unable to maintain the initial pedal rate. Gas exchange and heart rate (HR) were measured continuously using a breath-by-breath gas analysis system (K4b2, COSMED, Rome, Italy). Subjective strain was measured immediately after the final stage by the Borg Category Scale for Rating of Perceived Exertion.[14] Patients were asked to indicate how strenuous they had experienced the test by giving a number from 0 (no effort at all) to 10 (maximal effort). Aerobic capacity

was defined as the mean oxygen uptake during the last 30 seconds of exercise [VO_{2peak}, in $ml \cdot kg^{-1} \cdot min^{-1}$ and in ml·kg fat-free $mass^{-1} \cdot min^{-1}$ ($ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$)]. In addition, the ventilatory anaerobic threshold (VAT, expressed as percentage of predicted VO_{2peak}) was estimated by the ventilatory equivalent method, when V_E/VO_2 and $PetO_2$ increased while V_E/VCO_2 and $PetCO_2$ remained stable.[15, 16]

Finally, patients performed the submaximal 6-minute walk test (6MWT).[17] Patients were instructed to walk, not run, as far as they could along a 30-meter marked tape in a hall during a 6-minute period. Standardized encouragement was provided with the following phrases: "You are doing well" and "Keep up the good work". Patients were allowed to stop and rest during the test, but were instructed to resume walking as soon as they felt able to do so. The 6-minute walk distance (6MWD) was registered.

Physical fitness: Muscle strength

Isokinetic muscle strength of the knee extensors was assessed in both legs by a Biodex® dynamometer (Shirley, New York, USA), recording strength as torque in Newton meters (Nm). The patients were seated against a back-rest, firmly strapped at the hip and thigh. The rotational axis was aligned with the lateral femoral epicondyle. After five familiarization repetitions, isokinetic strength was measured at 60°/s with five maximal contractions and at 180°/s with 15 maximal contractions. Strong verbal encouragement was given during the test. Peak Torque (PT) was defined as the maximum torque generated by the patients throughout one series of repetitions at each velocity.

Physical fitness: Body composition

Height and body mass were measured without shoes. Body mass was measured using a Cormier Paribel® weighing chair (FH Balances Cormier, Romainville, France). Body mass index (BMI, $kg \cdot m^{-2}$) was calculated from height and body mass. Waist circumference (cm) was measured mid-way between the lowest rib and the iliac crest while standing. Thickness of four skinfolds (biceps, triceps, subscapular, suprailiaca region) was measured twice at the right side of the body with a Harpenden Skin-Fold Caliper (Burgess Hill, United Kingdom). The mean of the two measurements was used as representative for each site. Percentage body fat (BF) was predicted from skinfold thickness according to the method of Durnin and Womersley.[18]

Severity of fatigue

Severity of fatigue was assessed by the Dutch version of the Fatigue Severity Scale (FSS).[13] The FSS is a self-administered questionnaire with answers ranging from 1 ('strongly disagree') to 7 ('strongly agree'). The mean score of the nine inquiries ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Internal consistency, reliability, validity, and sensitivity of the FSS have been established in several patient groups.[13, 19]

In addition to the FSS, severity of fatigue was assessed with a horizontal visual analogue scale (VAS). Patients were asked to mark the 100-mm line according to how intense they had experienced fatigue during the last month (0 denotes 'no fatigue experienced' and 100 denotes 'the most severe fatigue').[20] Visual analogue scales have been found to yield reliable and valid data.[21, 22]

Health-related quality of life

HRQoL was assessed by the validated Dutch version (RAND-36)[23] of the Medical Outcomes Study Short Form-36 (SF-36).[24] The SF-36 is a validated, self-administered questionnaire used internationally to measure health status with respect to different dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, pain, mental health, vitality, general health perception, and change in perceived health during the last 12 months. All raw scores were converted to a 0 to 100 scale, with higher scores indicating higher levels of functioning or well-being.

Procedure

On the day of the measurements, patients refrained from caffeine, nicotine and heavy exercise. The order of the tests was standardized: patients started with the 6MWT, followed by the questionnaires (completed under supervision of the researcher), body composition measurements, strength test and finally the progressive maximal aerobic test. Exercise tests were performed under supervision of a physician. There were sufficient rest periods between the tests.

Statistics

Statistical analysis was performed using SPSS 10.1 for Windows (SPSS Inc., Chicago, IL, USA). Results are presented as mean ± standard deviation (SD), range or numbers. Results on aerobic capacity were compared to normative values for sedentary persons and to normative values for people who exercise no more than 1-2 hours a week (recreational).[25] Results on muscle strength were compared with the normative values of Akima et al.[26] and 6MWD was compared with the normative values of Enright & Sherill in healthy adults aged 40 to 80 years.[27] When patients were younger than 40 years, the normative values of Gibbons et al.[28] were used. Obesity was defined as a BMI ≥ 30, a waist circumference ≥ 102 cm in men and ≥ 88 cm in women or percentage BF ≥ 25% in men and ≥ 32% in women.[29-31]

Differences in physical fitness between patients and normative values were tested with the non-parametric Mann-Whitney U Test. Relationships between physical fitness and severity of fatigue, and between physical fitness and quality of life were explored using the non-parametric Spearman correlation coefficient (r). A probability value $p \leq .05$ determined statistical significance. However, because of the relatively small study sample, also results on the $\alpha = .10$ level are presented (indicating a trend).

Results

Physical fitness

Mean score on the Borg Scale was 6.3 ± 2.2, indicating that the patients experienced the maximal ergometer test on average as heavy to very heavy. The mean HRmax was 90 ± 10% of what was predicted (predicted HRmax = 220-age).[32]

The individual results of the patients are presented in Table 2. Table 3 shows the aerobic capacity and muscle strength of the patients compared with normative values. VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$ was 15 ± 22% (p= .07) and 34 ± 15% (p= .00) lower than normative values for, respectively, sedentary persons and those who exercise recreationally. VO_{2peak} in $ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$ was 16 ± 19.2% (p= .02) and 33 ± 14.8% (p= .00) lower than normative values for, respectively, sedentary persons and those who exercise recreationally. 6MWD was 16 ± 14% (p= .01) lower than normative values. There was no significant deficit in muscle strength. Table 4 shows the body composition of the LTx group. According to the cut-off points for obesity based on

Table 2. Individual results on physical fitness in the 18 liver transplant recipients

Age (year/ Gender)	BMI ($kg \cdot m^{-2}$)	Waist (cm) [a]	Body fat (%) [b]	VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	VO_{2peak} ($ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$) [b]	VAT (% predicted VO_{2peak}sed)	VAT (% predicted VO_{2peak}recr)	6MWD (m)	PT extension 60°/sec (Nm)	PT extension 180°/sec (Nm)
56/M	28.3	111.0	29.0	36.5	51.4	54.1	42.7	652	156.3	88.2
52/M	29.0		32.7	16.7	24.8	49.1	38.9	428	101.8	73.1
42/F	22.8		28.9	34.5	48.5	90.5	65.8	530	100.0	65.6
60/F	38.4	118.5	42.0	13.1	22.5	43.6	32.5	495	101.9	78.6
64/M	29.7	103.5	30.6	21.7	31.3	77.4	55.4	430	99.9	62.6
24/F	21.0	72.0	25.9	29.9	40.4	38.8	31.1	660	159.9	111.5
46/M	26.5	100.0	25.8	28.2	38.0	48.6	38.7	606	151.6	88.5
63/M	24.4		20.5	20.9	26.4	69.4	49.7	410	74.4	44.8
42/M	34.9	132.0		22.8		30.9	25.8	513	145.9	118.3
53/F	23.9	77.5	30.1	23.1	33.0	108.6	64.8	465	40.0	35.7
53/M	25.9	99.6	23.6	20.7	27.1	56.7	42.6	510	149.3	96.8
39/M	23.7	87.0	17.4	31.2	37.8	51.5	43.5	547	169.0	111.8
33/M	24.0	88.0	19.8	35.1	43.7	67.9	59.9	510	155.9	116.9
63/F	33.0	103.0	34.8	15.8	24.2	57.9	43.2	303	67.2	39.4
45/F	26.8		30.8	23.6	34.1	61.0	46.2	514	120.1	61.7
39/F	18.7	75.0	22.7	30.2	38.1	56.2	46.8	600	115.9	67.9
32/M	22.9	91.0	20.4	25.0	31.4	43.4	38.3	576	180.4	124.6
58/M	25.1	99.0	25.0	18.5	24.6	48.6	37.9	495	128.6	91.9

Abbreviations: BMI ($kg \cdot m^{-2}$), body mass index; Waist (cm), waist circumference; VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$), peak oxygen uptake per kg; VO_{2peak} ($ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$), peak oxygen uptake per kg fat-free mass; VAT (% predicted VO_{2peak}), ventilatory anaerobic threshold as percentage of predicted VO_{2peak}; sed, sedentary normative values; recr, recreational normative values (people who exercise more than 1 to 2 hours a week); 6MWD, six-minute walk distance; PT, peak torque

[a] Waist circumference: n=14, because of thickness of the skin at the place of the cicatrice in four patients

[b] Body fat and VO_{2peak}: n=17, because the thickness of the subscapular skinfold could not be measured reliably in one patient

Table 3. Aerobic capacity and muscle strength in the liver transplant group

	LTx group	Norm values [a]		p-value
Aerobic capacity				
VO_{2peak} (ml·kg^{-1}·min^{-1})	24.8 ± 6.9	29.4 ± 7.4	(sed)	.07†
		37.5 ± 6.7	(recr)	.00*
VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1}) [b]	34.0 ± 8.7	41.0 ± 7.8	(sed)	.00*
		50.9 ± 5.9	(recr)	.00*
6MWD (m)	513.6 ± 88.9	609.6 ± 97.6		.01*
Muscle strength				
PT extension at 60°/sec (Nm)	123.2 ± 38.7	138.5 ± 44.1		.22
PT extension at 180°/sec (Nm)	82.1 ± 27.9	86.1 ± 30.1		.59

Results are presented as mean ± SD

Abbreviations: VO_{2peak} (ml·kg^{-1}·min^{-1}), peak oxygen uptake per kg; VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1}), peak oxygen uptake per kg fat-free mass; sed, sedentary normative values; recr, recreational normative values (people who exercise no more than 1 to 2 hours a week); 6MWD, six-minute walk distance; PT, peak torque

[a] Vos et al. 2001; Enright & Sherill 1998; Gibbons et al. 2001; Akima et al. 2001

[b] n=17, because the thickness of the subscapular skinfold could not be measured reliably in one patient

* Significant (p≤ .05) difference between patients and normative values

† Difference between patients and normative values at the α= .10 level (trend)

Table 4. Body composition in the liver transplant group

Body composition	Mean ± SD
Body weight (kg)	80.6 ± 18.3
Height (m)	1.74 ± .11
Body Mass Index (kg·m^{-2})	26.6 ± 5.0
Waist circumference (cm) [a]	96.6 ± 16.8
Body fat (%) [b]	26.9 ± 6.4

Results are presented as mean ± SD

[a] Waist circumference: n=14, because of thickness of the skin at the place of the cicatrice in four patients

[b] Body fat: n=17, because the thickness of the subscapular skinfold could not be measured reliably in one patient

BMI, waist circumference, and percentage BF, respectively 17%, 36% and 41% of the patients were classified as obese.

Relationships

Table 5 shows the correlation coefficients between the physical fitness parameters and severity of fatigue as assessed with the FSS and VAS. None of the parameters of muscle strength or body composition were significantly related with severity of fatigue, assessed with either the FSS or the VAS.

VO_{2peak} in $ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$ (absolute and expressed as percentage of recreational normative values) and 6MWD (absolute) were related with severity of fatigue as assessed with the FSS at the $\alpha = .10$ level (trend). With respect to the VAS, VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$ (absolute and expressed as percentage of recreational normative values), VO_{2peak} in $ml \cdot kg_{FFM}^{-1} \cdot min^{-1}$ (absolute and expressed as percentage of both sedentary and recreational normative values) and 6MWD (absolute and expressed as percentage of normative values) were significantly ($p \leq .05$) correlated with severity of fatigue. VO_{2peak} in $ml \cdot kg^{-1} \cdot min^{-1}$ as percentage of sedentary normative values was related with severity of fatigue as assessed with the VAS at the $\alpha = .10$ level (trend). The VAT was not correlated with severity of fatigue, assessed with the FSS or the VAS.

Table 6 shows the correlation coefficients between physical fitness parameters and HRQoL. There were several significant correlations between physical fitness and HRQoL, and particularly between aerobic capacity on the one hand, and 'Physical functioning', 'Social functioning', and 'Vitality' on the other.

Discussion

This is the first study in which relationships between several aspects of physical fitness and severity of fatigue are explored after LTx. The study is an initial step in identifying factors that are associated with fatigue in liver transplant recipients. A limitation of this study may be that the sample was relatively small. However, we believe that this sample is representative for patients after LTx, and that the study provides important information for the development of rehabilitation programs for liver transplant recipients.

Table 5. Spearman correlation coefficients for the relationships between fitness parameters and severity of fatigue as measured with the Fatigue Severity Scale (FSS) and the Visual Analogue Scale (VAS) in 18 liver transplant recipients

Physical fitness	Fatigue			
	FSS		VAS	
	r	p-value	r	p-value
Aerobic capacity				
VO_{2peak} (ml·kg^{-1}·min^{-1})	-.40	.10	-.52	.03*
% of sedentary norm	-.17	.50	-.42	.08†
% of recreational norm	-.32	.20	-.53	.03*
VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1})[a]	-.43	.08†	-.51	.04*
% of sedentary norm	-.35	.17	-.50	.04*
% of recreational norm	-.45	.07†	-.61	.01*
VAT (% predicted VO_{2peak} sed)	.22	.38	.03	.92
VAT (% predicted VO_{2peak} recr)	.17	.49	-.06	.82
6MWD (m)	-.44	.07†	-.53	.03*
% of norm	-.25	.32	-.52	.03*
Muscle strength				
PT extension at 60°/sec (Nm)	-.39	.11	-.31	.22
% of norm	-.15	.56	-.28	.27
PT extension at 180°/sec (Nm)	-.30	.22	-.12	.64
% of norm	.02	.93	.04	.87
Body composition				
Body Mass Index (kg·m^{-2})	.03	.91	.06	.82
Waist circumference (cm)[b]	-.07	.82	-.06	.83
Body fat (%)[a]	.32	.21	.15	.58

Abbreviations: VO_{2peak} (ml·kg^{-1}·min^{-1}), peak oxygen uptake per kg; VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1}), peak oxygen uptake per kg fat-free mass; VAT (% predicted VO_{2peak}), ventilatory anaerobic threshold as percentage of predicted VO_{2peak}; sed, sedentary normative values; recr, recreational normative values (people who exercise no more than 1 to 2 hours a week); 6MWD, six-minute walk distance; PT, peak torque

[a] n=17, because the thickness of the subscapular skinfold could not be measured reliably in one patient

[b] n=14, because of thickness of the skin at the place of the cicatrice in four patients

* Significant ($p \leq .05$) correlation

† Correlation at the $\alpha = .10$ level (trend)

Table 6. Spearman correlations coefficients for the relationships between physical fitness and health-related quality of life as assessed with the RAND-36 in 18 liver transplant recipients

Physical fitness	RAND-36 domain								
	PF	SF	Rlp	Rle	MH	VT	BP	GH	CH
Aerobic capacity									
VO_{2peak} (ml·kg^{-1}·min^{-1})	**.55**	-	-	-	-	-	-	-	-
% of sedentary norm	-	.42	-	-	-	**.50**	-	-	-
% of recreational norm	**.48**	-	-	-	-	**.51**	-	-	-
VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1})[a]	**.57**	**.51**	.41	-	-	-	-	-	-
% of sedentary norm[a]	-	**.56**	-	-	-	**.59**	-	.48	-
% of recreational norm[a]	.46	**.58**	-	-	-	**.58**	-	-	-
VAT (% predicted VO_{2peak} sed)	-	-	-	-	-	-	-	-	-
VAT (% predicted VO_{2peak} recr)	-	-	-	-	-	-	-	-	-
6MWD (m)	**.67**	**.57**	-	-	.53	-	**.54**	-	-
% of norm	-	**.70**	-	-	-	**.51**	-	-	.44
Muscle strength									
PT extension at 60°/sec (Nm)	.44	-	-	-	.41	-	-	-	-
% of norm	-	**.68**	-	-	-	-	**.56**	-	-
PT extension at 180°/sec (Nm)	-	-	-	-	-	-	.44	-	-
% of norm	-	**.51**	-	**.54**	-	-	**.50**	-	-
Body composition									
Body Mass Index (kg·m^{-2})	-	-	-	-	-	-	-	-	-
Waist circumference (cm)[b]	-	-	**-.49**	-.41	-	-	-	-	-
Body fat (%)[a]	-	-	-	-	-	-	-	-	-

To enhance the clarity of the table, only significant correlation coefficients (p≤ 0.05, bold) or trends (p< 0.10, not bold) are presented

Abbreviations: VO_{2peak} (ml·kg^{-1}·min^{-1}), peak oxygen uptake per kg; VO_{2peak} (ml·kg$_{FFM}^{-1}$·min^{-1}), peak oxygen uptake per kg fat-free mass; VAT (% predicted VO_{2peak}), ventilatory anaerobic threshold as percentage of predicted VO_{2peak}; sed, sedentary normative values; recr, recreational normative values (people who exercise no more than 1 to 2 hours a week); 6MWD, six-minute walk distance; PT, peak torque; PF, physical functioning; SF, Social functioning; Rlp, Role limitations physical; Rle, Role limitations emotional; MH, mental health; VT, vitality; BP, bodily pain; GH, general health perception; CH, changes in health

[a] n=17, because the thickness of the subscapular skinfold could not be measured reliably in one patient

[b] n=14, because of thickness of the skin at the place of the cicatrice in four patients

Physical fitness

We found average deficits in VO_{2peak} of 16% to 34%, when we compared the results in the liver transplant recipients with normative values for, respectively, sedentary persons and those who exercise no more than 1-2 hours a week. We believe that a value in between the sedentary and recreational normative values is representative for healthy Dutch persons of the same age as the liver transplant recipients that participated in our study. 6MWD was 16% lower than normative values. This subnormal level of aerobic capacity (both VO_{2peak} and 6MWD) is in agreement with findings of previous studies.[10-12] Furthermore, the prevalence of obesity was higher in this study than in the general Dutch population; 17% of the patients had a BMI of more than 30 compared to 10% in the general Dutch population.[33]

Impaired aerobic capacity in liver transplant recipients may be due to the use of immunosuppressive medication, e.g. glucocorticoids and calcineurin inhibitors, which may influence both the cardiovascular system and skeletal muscles.[34, 35] Immunosuppressive medication can also induce appetite stimulation and diabetes mellitus; this in association with emotional conditions can cause a change in eating habits.[36, 37] Furthermore, patients with primary biliary cirrhosis and some patients with other chronic liver disease are hypermetabolic. LTx in these patients may lead to a reduction in resting metabolic rate, and can also cause an increase in BF.[37, 38] Besides immunosuppressive medication and changes in appetite and metabolism, also deconditioning (both before and after transplantation) may contribute to the impaired aerobic capacity and body composition.[39, 40] In a previous study we found that severe complaints of fatigue were associated with low levels of everyday physical activity in liver transplant recipients.[9]

Because of the immunosuppressive medication and deconditioning, we also expected a deficit in muscle strength. However, this was not demonstrated in the present study, in contrast to Beyer et al.[10], who found a 10 to 20% lower muscle strength in liver transplant recipients compared to age- and sex-matched sedentary individuals. They contributed this deficit to muscle weakness as a side-effect of glucocorticoids. The discrepancy between the findings of our study and those of Beyer et al.[10] may be explained by the use of Tacrolimus instead of cyclosporine in the majority of our subjects. Tacrolimus is known to have less side-effects than cyclosporine.[41]

Stephenson et al.[11] reported an early VAT in liver transplant recipients (<45-50% of the predicted VO_{2max}) compared to 50-60% of the VO_{2max} in healthy persons found

by Davis et al.[42] They contributed this early anaerobic threshold in liver transplant recipients to the cyclosporine-induced decrease in mitochondrial oxygen consumption.[11] However, the European Respiratory Society[43] reported that there is a wide range of normal predicted values (35-70%). Therefore, it is difficult to indicate whether the VAT in our patients was reduced compared to normal (58.6 ± 18.9% and 44.7 ± 11.1% of predicted VO_{2max} for, respectively, sedentary persons and those who exercise recreationally).

Physical fitness and severity of fatigue

Although relationships between severity of fatigue (as measured with the FSS and VAS) and physical fitness were not univocal, this study demonstrates a relationship between aerobic capacity and severity of fatigue after LTx. Patients with more severe complaints of fatigue had larger deficits in aerobic capacity than patients with less severe complaints of fatigue. Although this cross-sectional study does not allow us to conclude that a reduced aerobic capacity results in fatigue (or vice versa), there may be an interaction between parameters: complaints of fatigue leading to decreased physical activity[9] and decreased physical fitness, leading to further deterioration of complaints of fatigue. It may then be hypothesized that rehabilitation programs, aimed at enhancing aerobic capacity, can be effective in breaking through this negative spiral, and (partly) reduce complaints of fatigue in this population. However, this hypothesis has to be confirmed in future randomized trials.

In contrast to our expectations, the present study indicates that other aspects of physical fitness, muscle strength and body composition, do not seem to be related with severity of fatigue after LTx. However, it should be realized that our study sample was relatively small and some of the studied relationships may have failed to show statistical significance.

Physical fitness and HRQoL

Previous studies on healthy persons indicate that physical activity, fitness, and body fatness are associated with HRQoL and mood.[44, 45] There are also indications that physical activity is related to HRQoL after LTx.[9, 46] Therefore, we expected to find a relationship between physical fitness and HRQoL in our study group. In agreement with the study of Stewart et al.[45] in healthy elderly subjects, we found several significant

correlations between physical fitness (particularly aerobic capacity) and HRQoL in our liver transplant recipients. Patients with large deficits in physical fitness experienced worse HRQoL than patients with small deficits in physical fitness. However, in contrast with studies in healthy persons[44, 45], we found only few relationships between body composition and HRQoL.

Our results on the relationships between physical fitness and HRQoL imply that rehabilitation programs aimed at improving physical fitness (particularly aerobic capacity) may consequently result in improved HRQoL, particularly in improved physical and social functioning, vitality, and bodily pain. However, these implications have to be confirmed in future randomized trials on the effects of such rehabilitation programs in liver transplant recipients.

Conclusion

Aerobic capacity in the liver transplant recipients was distinctly impaired, and the prevalence of obesity was higher than in the general population. There were no indications that muscle strength is impaired after LTx. Based on the relationships we found between aerobic capacity and severity of fatigue, a rehabilitation program aimed at enhancing aerobic capacity may help in reducing complaints of fatigue after LTx. Such rehabilitation programs may also result in improved HRQoL.

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Chapter 5

Fatigue, level of everyday physical activity and quality of life after liver transplantation

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Abstract

Objective To assess whether liver transplant recipients have a hypoactive (sedentary) lifestyle, and whether the level of everyday physical activity is related to complaints of fatigue. In addition, we explored the relationship between activity level and health-related quality of life (HRQoL).

Design Case comparison.

Subjects Eight persons 6-36 months after liver transplantation with varying severity of fatigue and eight persons without known impairments (matched for gender, age, social situation, and employment).

Methods Activity levels were assessed during two randomly selected consecutive weekdays with an accelerometry-based Activity Monitor. In the transplantation group, also severity of fatigue (Fatigue Severity Scale, FSS) and HRQoL (RAND-36) were assessed.

Results Five liver transplant recipients had a hypoactive lifestyle, but there was no significant difference in activity level between the transplantation group and comparison group. Severity of fatigue was correlated ($p = .01$) with both duration of dynamic activities and intensity of everyday activity ($r = -.81$ and $r = -.84$, respectively). Activity level was correlated ($p \leq .05$) with several domains of HRQoL ($r = .72$ to $r = .78$).

Discussion As a group, liver transplant recipients were not significantly less active than comparison subjects. Activity level was related with severity of fatigue and HRQoL. These findings have implications for the development of interventions needed to rehabilitate persons after liver transplantation.

Introduction

Liver transplantation has become a commonly used treatment for end-stage liver disease and acute liver failure, and both survival and liver function are markedly improved after transplantation.[1, 2] However, liver transplant recipients often experience fatigue.[3-5] In a prospective study, Gross et al.[5] showed that, although the intensity of fatigue was reduced compared with prior liver transplantation, fatigue remained the most distressing symptom one year after the transplantation. In a previous study by our group, complaints of severe fatigue were found in 44% of persons up to 15 years after liver transplantation, and these complaints did not tend to decrease over time.[6] In most cases, the cause for fatigue is unknown.

Knowledge of the underlying mechanisms of fatigue after liver transplantation is a prerequisite for the development of interventions needed to successfully rehabilitate liver transplant recipients. In a recent study, Aadahl et al.[2] suggested that, after liver transplantation, recipients experience physical fatigue and reduced activity rather than reduced motivation and mental fatigue.

The aims of the study were to assess whether liver transplant recipients have a hypoactive (sedentary) lifestyle, and whether the level of everyday physical activity in this group is related to the severity of fatigue. Also explored were relationships between the level of everyday physical activity on the one hand and health-related quality of life (HRQoL) and time post-transplantation on the other.

Methods

Subjects

Eight liver transplant recipients with varying severity of fatigue (ranging from 'no signs of fatigue' to 'most disabling fatigue'), as assessed with the Fatigue Severity Scale (FSS) of Krupp et al.[7] (see below), were recruited from the outpatient clinic of the Erasmus University Medical Center. Inclusion criteria were: liver transplantation 6-36 months previously, adequate knowledge of the Dutch language, age between 18 and 65 years. Exclusion criteria were: multiorgan transplant recipients, comorbidity that might interfere with everyday physical activity, hypersensitivity for adhesive materials.

Because no sufficient reference values are available on everyday physical activity as measured with our Activity Monitor (AM), each liver transplant recipient was matched for gender, age (± 3 years), social situation (living alone, living with a partner) and, if applicable, for employment situation (full-time/part-time/unemployed) and type of work (physically active/physically passive) with a subject without known impairments. In case the employment situation or type of work had changed compared with the situation before transplantation (or liver disease) as a consequence of the transplantation (or liver disease), these matching criteria were not used. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center. Written informed consent was obtained from all subjects.

Instruments

Level of everyday physical activity

For assessment of the level of everyday physical activity an AM (size: 15x9x3.5 cm; weight 500 g; Temec Instruments BV, Kerkrade, The Netherlands) was used. The AM is based on long-term (more than 24 hours) ambulatory monitoring of signals from body-fixed accelerometers, and consists of four accelerometers, a portable data recorder and a computer with analysis programs.[8] From the accelerometer signals, the duration, rate, and moment of occurrence of activities associated with mobility (the stationary activities lying, sitting, and standing; the dynamic activities walking

(including climbing/descending stairs and running), cycling, wheelchair-driving, general (non-cyclic) movement), and transitions between postures can be detected with a one-second resolution. Furthermore, information on the variability of the acceleration signal (motility) can be obtained, which is related to the intensity of body-segment movements.[9-11] Validity studies, in which simultaneously made videotaped registrations (reference method) were compared with the outcome of the AM, have shown that the AM is valid to quantify activities associated with mobility.[8] Furthermore, the AM can detect differences in the level of physical activity during everyday life between groups, which supports its validity and applicability in clinical research.[12-14]

Four ADXL202 uniaxial piezo-resistive accelerometers were used (Analog Devices, Breda, The Netherlands, adapted by Temec Instruments, Kerkrade, The Netherlands; size: 1.5x1.5x1 cm). One accelerometer was attached to each thigh (while standing, sensitive in anteroposterior direction), and two were attached to the skin over the sternum (while standing, one accelerometer is sensitive in anteroposterior direction and one is sensitive in longitudinal direction). The accelerometers were connected to the AM, which was worn in a padded bag around the waist. Accelerometer signals were stored digitally on a PCMCIA flash card with a sampling frequency of 32 Hz. After the measurement, data were downloaded onto a computer for analysis by the Kinematic Analysis part of the Vitagraph Software[15] (supplied by Temec Instruments BV, Kerkrade, The Netherlands). A detailed description of the activity detection procedure has been described previously.[8, 12] Motility signals are averaged to calculate the body motility. This measure is assumed to be related to the overall level or intensity of physical activity during the measurement.

Subjects wore the AM during 48 hours. Data of the AM measurement were calculated per day (24-hour period) and the following variables were assessed: duration of dynamic activities (composite measure: walking (including climbing/descending stairs and running), cycling, general movement), as percentage of a 24-hour period; number of transitions (contains all transitions except the lying transitions such as the transition from lying prone to lying supine); number of walking periods (>10 seconds). In addition, body motility was assessed, addressing mean motility over a 24-hour period (respresenting intensity of everyday physical activity) and motility during walking (representing walking speed).

Severity of fatigue

For the assessment of severity of fatigue the Dutch version of the FSS was used.[7] The FSS is a nine-item self-administered questionnaire. The mean score of the nine inquiries ranges from 1 ('no signs of fatigue') to 7 ('most disabling fatigue'). Internal consistency, reliability, validity, and sensitivity of the FSS have been established in different groups.[7, 16]

Health-related Quality of Life

HRQoL was assessed with a validated Dutch version of the Medical Outcomes Study Short Form-36 (SF-36)[17], the RAND-36.[18] The SF-36 is a validated, self-administered questionnaire used internationally to measure health status with respect to different dimensions: physical functioning, social functioning, role limitations due to physical problems, role limitations due to emotional problems, pain, mental health, vitality, and general health perception.[19] Additionally, one single item assesses change in perceived health during the previous 12 months. All raw scale scores are linearly converted to a 0 to 100 scale, with higher scores indicating higher levels of functioning or well-being.

Protocol

Measurements with the AM were performed in both the liver transplant recipients and their comparison subjects during two randomly selected consecutive weekdays (48-hour measurement). To avoid measurement bias, subjects were instrumented with the AM in the home situation (natural behaviour). Furthermore, the principles of the AM were explained to the subjects only after the measurements. All subjects agreed with this procedure. Whenever possible, measurements with the AM in the liver transplant recipient were taken in the same week as those in his/her comparison subject but always within three weeks. Subjects were instructed to continue their ordinary daily life; however, subjects were not allowed to swim or take a bath or shower.

Severity of fatigue and HRQoL were assessed only in the transplantation group. The FSS and RAND-36 were completed by the liver transplant recipients in the home situation (before the instrumentation of the AM), under supervision of a researcher.

Statistics

Statistical analysis was performed using SPSS 10.1 for Windows. Data are presented as mean with standard deviation (SD) unless otherwise indicated. The AM parameters 'duration of dynamic activities' (composite measure: walking (including climbing/descending stairs and running), cycling, and general movement; as percentage of a 24-hour period) and 'mean motility' were used to explore relationships between the level of everyday physical activity on the one hand and severity of fatigue, time post-transplantation, and HRQoL on the other. Hypoactivity was defined as the mean duration of dynamic activities (percentage of a 24-hour period) in the comparison group minus two times the SD. Comparisons between data were made using the Wilcoxon test for paired observations, and the Mann-Whitney U test or the Chi-square test for unpaired observations. Using the Spearman correlation coefficient (r) relationships between parameters were studied. A probability value $p \leq .05$ determined statistical significance. However, because of the small study population, also results on the $\alpha = 0.10$ level are presented (trend).

Results

General characteristics of the study population are given in Table 1. In both groups, four men and four women were included. There were no differences in any of the physical characteristics between the study groups. However, more than half of the employed comparison subjects had a full-time job, whereas all employed liver transplant recipients had a part-time job ($p = .04$) as a consequence of the liver disease or transplantation. Furthermore, all employed comparison subjects had physically passive jobs, whereas two of the employed liver transplant recipients had physically active jobs ($p = .07$). Three liver transplant recipients were unemployed, two of them as a consequence of the liver disease.

Table 2 presents medical characteristics of the liver transplant recipients and their score on the FSS. The mean (SD) duration of liver disease prior to transplantation was 6.5 (4.9) days for the acute conditions and 12.4 (6.1) years for the chronic conditions; mean (SD) time post-transplantation was 20.8 (7.3) months. Mean (SD) score on the FSS was 3.8 (1.4).

Table 1. General characteristics of the liver transplant recipients and comparison subjects

	LTx recipients (n=8)	Comparison subjects (n=8)	p-value
Age (yr)	46 (11)	48 (11)	.46
Body mass (kg)	82.3 (13.7)	79.4 (13.2)	.64
Height (m)	1.76 (.10)	1.72 (.05)	.46
Body mass index	26.7 (4.1)	26.6 (4.4)	.92
Employment situation			
employed/unemployed	5/3	7/1	.25
full-time/part-time	0/5	4/3	.04*
Type of work			
(active/passive)[a]	2/3	0/7	.07†
Social situation			
(living alone/living with a partner)	0/8	1/7	.30

Results are mean (SD) or numbers

[a] active/passive: 'active' and 'passive' denote physically active ('blue-collar') and physically non-active ('white-collar') work

*significantly different ($p \leq .05$) between groups

†different between groups at the $\alpha = .10$-level (trend)

Table 2. Medical characteristics of the 8 liver transplant recipients and their scores on the Fatigue Severity Scale (FSS)

Sex/Age (years)	Indication for transplantation	Acute/ Chronic	Duration liver disease prior to transplantation	Time post-transplantation (months)	Score on FSS
M/55	Hepatitis B	Chronic	15 years	21	2.9
F/46	Acute liver failure	Acute	3 days	19	4.6
F/22	Atretic bile duct	Chronic	22 years	17	3.2
F/52	Acute liver failure	Acute	10 days	24	5.1
M/45	Primary sclerosing cholangitis	Chronic	13 years	11	2.2
F/44	Polycystic liver disease	Chronic	10 years	15	2.8
M/53	Hepatitis B	Chronic	3.5 years	24	2.9
M/51	Primary sclerosing cholangitis	Chronic	11 years	35	6.3

Level of everyday physical activity and correlation with severity of fatigue

In both groups there was no difference in the duration of dynamic activities between the first and second 24-hour part of the measurements with the AM (liver transplant recipients: 10.2 (5.2)% and 10.3 (3.2)%, respectively, p= .58; comparison subjects: 12.1 (1.7)% and 13.1 (1.7)%, respectively, p= .31). Therefore, the data from the AM measurements were averaged over the two consecutive days (Table 3). None of the outcome measures between the two groups reached statistical significance. There was a trend (p= .07) that the liver transplant recipients had less walking periods than their comparison subjects. The duration of dynamic activities (as percentage of a 24-hour period) corresponds with 147 minutes per day in the liver transplant recipients and with 181 minutes per day in the comparison subjects. Five of the eight liver transplant recipients were classified as hypoactive (i.e. the two persons with acute liver failure, and three persons with chronic liver disease prior to transplantation).

Severity of fatigue was correlated with both duration of dynamic activities (as percentage of a 24-hour period) and mean motility (r= -.81, p= .01 and r= -.84, p= .01, respectively; Figure 1).

Table 3. Everyday physical activity as measured with the Activity Monitor in 8 liver transplant recipients and 8 comparison subjects

	LTx Recipients (n=8)	Comparison subjects (n=8)	p-value
Duration of dynamic activities (%) [a]	10.2 (3.8)	12.6 (0.9)	.23
Mean motility (g) [b]	.023 (.007)	.029 (.007)	.13
Motility during walking (g) [c]	.164 (.015)	.172 (.024)	.57
Transitions (number) [d]	119 (26)	121 (26)	.96
Walking periods > 10s (number)	155 (54)	197 (35)	.07*

Data are calculated per day and are presented as mean (SD) over the 2 measurement days

[a] Duration of dynamic activities: composite measure (walking, cycling, general movement) expressed as percentage of a 24-h period

[b] Mean motility: represents intensity of everyday physical activity (1g = 9.81 $m \cdot s^{-2}$)

[c] Motility during walking: represents walking speed

[d] Transitions: contains all transitions except the lying transitions such as the transition from lying prone to lying supine

* Difference between groups at the α= .10 level (trend)

Correlation between level of everyday physical activity, time post-transplantation, and HRQoL

At the α= .10 level, time post-transplantation was inversely correlated with mean motility (r= -.64, p= .09) (Figure 2). The relationship between time post-transplantation and duration of dynamic activities was not significant (r= -.61, p= .11).
Table 4 presents correlation coefficients between HRQoL and level of everyday physical activity. The domains 'Physical function', 'Role-emotional', and 'Mental health' were correlated with the duration of dynamic activities and mean motility (p≤ .05 and p≤ .10).

Table 4. Spearman correlation coefficients for the relationships between health-related quality of life as assessed with the RAND-36 on the one hand and duration of dynamic activities [a] and mean motility [b] on the other, in 8 liver transplant recipients

RAND-36 domain	Scores on RAND-36	Relation with duration dynamic activities		Relation with mean motility	
	Mean (SD)	r	p-value	r	p-value
Physical function	86.3 (11.6)	.72	.04*	.75	.03*
Social functioning	73.3 (22.8)	.35	.40	.48	.23
Role-Physical	59.4 (35.2)	.25	.55	.38	.36
Role-Emotional	75.0 (46.3)	.63	.09†	.76	03*
Mental health	78.0 (15.9)	.72	.05*	.78	.02*
Vitality	68.8 (18.1)	.46	.25	.59	.12
Bodily pain	76.8 (29.0)	.38	.35	.50	.20
General health	56.9 (8.0)	.68	.15	.72	.16
Changes in health	81.3 (22.2)	.21	.63	.21	.63

Results are mean (SD).
[a] duration dynamic activities: composite measure (walking, cycling, general movement) expressed as percentage of a 24-h period
[b] mean motility: represents intensity of everyday physical activity (1 g=9.81 m/s-2)
* significant (p≤ .05) correlation
† correlation at α= .10-level (trend)

Figure 1. Correlations between severity of fatigue on the one hand, and duration of dynamic activities and mean motility on the other, in 8 liver transplant recipients

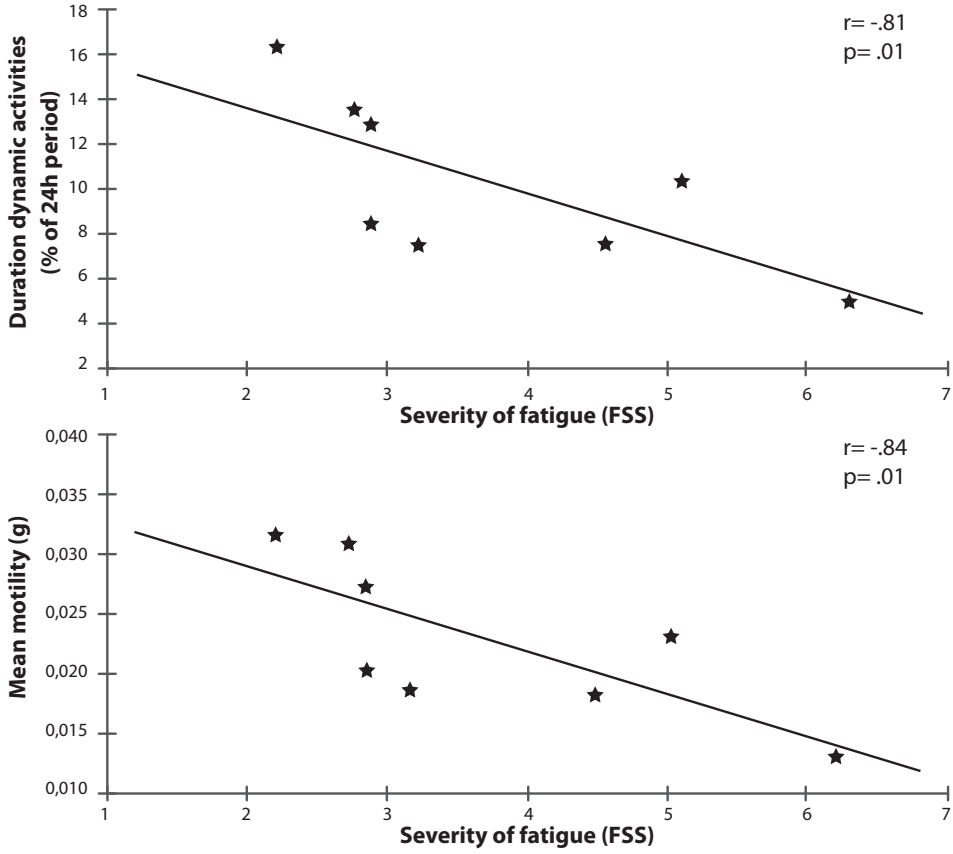
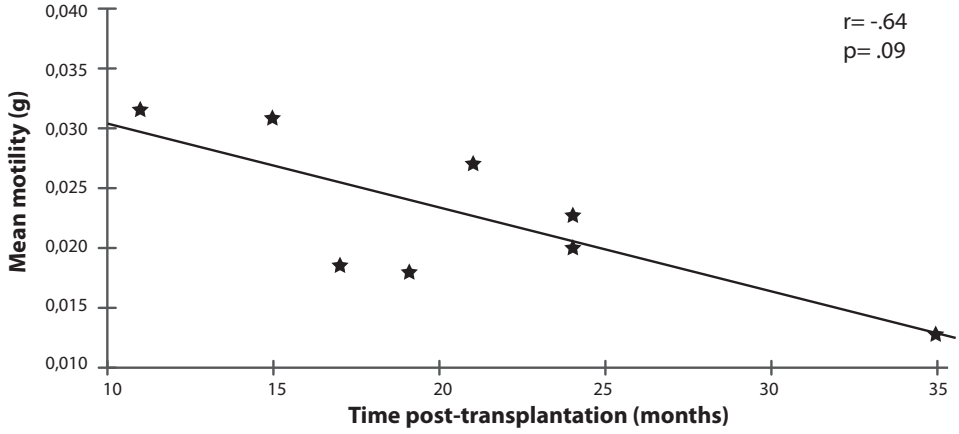


Figure 2. Relation between time post-transplantation and mean motility in 8 liver transplant recipients.



Mean motility represents intensity of everyday physical activity (1g = 9.81 $m \cdot s^{-2}$).

Discussion

To our knowledge, this is the first study in which levels of everyday physical activity are objectively and in detail determined in persons after liver transplantation. Despite the small study population, which is a limitation of the study, we believe that the study may help in the development of rehabilitation programs for liver transplant recipients.

To establish the consequences of liver transplantation on everyday physical activity in the most effective way, the comparison group was matched for physical characteristics (age, gender), social situation, employment situation, and type of work. All employed liver transplant recipients had part-time jobs whereas most of the employed comparison subjects had full-time jobs (Table 1). However, because the lower employment rate in the transplantation group was a consequence of the transplantation (or liver disease), our study groups were appropriately composed with respect to employment situation (matching criterion not applicable). Due to time considerations, it was not possible to match all comparison subjects for type of work (active/passive); however, we do not expect this discrepancy between the two groups (two liver transplant recipients had physically active jobs whereas all employed comparison subjects had physically passive jobs) to seriously affect the main findings.

The level of everyday physical activity as measured with the AM in the comparison group is in agreement with measurements with the AM in other groups without known impairments.[12-14] Thus, in the present study, the comparison group was not an exceptionally highly active group.

Severity of fatigue, level of everyday physical activity, and time post-transplantation

Although 5 of the 8 liver transplant recipients had a hypoactive lifestyle, no significant difference was found in the level of everyday physical activity between the transplantation group and the comparison group. This lack of significant difference may be due to the small study sample and also to the composition of the study sample. Because we wanted to obtain insight in the relationship between severity of fatigue and the level of everyday physical activity, also liver transplant recipients with no signs of fatigue were included. Based on the inverse relationship that we found between severity of fatigue and level of everyday physical activity, we expect that when more severely fatigued liver transplant recipients would have been included in the present

study, activity levels would have been found significantly lower in the patients than in their healthy comparison subjects.

Although this cross-sectional study does not allow to conclude that fatigue results in a hypoactive lifestyle (or vice versa), there may be an interaction between the two parameters: fatigue leading to hypoactivity, leading to a reduction in exercise capacity and increasing complaints of fatigue, leading to further hypoactivity. It may then be hypothesized that rehabilitation programs, aimed at enhancing levels of everyday physical activity, can be effective in breaking through this negative spiral of hypoactivity and (partly) reduce complaints of fatigue in this population. However, this hypothesis has to be confirmed in future randomized trials. Currently, a study is being performed by our group on the relationship between severity of fatigue and exercise capacity in liver transplant recipients.

Persons with acute liver failure may be less restricted in their everyday life after transplantation than persons with a chronic cause for liver transplantation, because no period of deconditioning has preceded the transplantation. However, in the present study, the two persons with acute liver failure were both classified as hypoactive. However, because of our small sample size, no conclusions can be drawn about possible differences due to liver transplantation on everyday life between acute and chronic conditions.

It may also be hypothesized that medication affects complaints of fatigue and as a consequence the level of everyday physical activity in liver transplant recipients. However, in a former study by our group on fatigue in a large sample of liver transplant recipients (n=96), no relationship was found between medication and severity of fatigue.[6]

Results of the present study seem to be in contrast to those of Nicholas et al.[20] who assessed mobility (ability to walk and climb stairs) and levels of physical activity (participation in sports) by means of questionnaires at least one year after liver transplantation. They concluded that, at least one year after transplantation, liver transplant recipients experience little difficulty with mobility and have high levels of physical activity. This discrepancy between their study and ours may be explained by differences in techniques used (questionnaire versus accelerometry-based AM; sports participation versus everyday physical activity) and differences in time post-transplantation. The study of Nicholas et al.[20] also included persons more than three years after liver transplantation, whereas the post-transplantation period in the present study ranged from six months to three years. However, the results of the

present study indicate that levels of everyday physical activity may not improve over time after liver transplantation; in fact, the inverse correlation (α= .10 level, Figure 2) found between time post-transplantation and mean motility (representing intensity of everyday activity) implies that liver transplant recipients become less intensively active over time. This finding agrees with a previous study by our group in 96 persons after liver transplantation, which showed no indication that fatigue improves over time.[6] Longitudinal studies in a large sample, monitoring subjects for long periods of time, are needed to confirm the effect of the post-transplantation period on everyday physical activity, as found in the present study.

Level of everyday physical activity and HRQoL

In comparison with norm values of the RAND-36 for the Dutch population[19], our liver transplant recipients scored low on the domains 'Social functioning', 'Role-Physical', 'Role-Emotional', and 'General health'. These results are in agreement with the study of Aadahl et al.[2] investigating a group of recipients one to three years after liver transplantation. In the present study the correlations found between the level of everyday physical activity and domains of HRQoL ('Physical function', 'Role-Emotional', 'Mental health', Table 4) seem to confirm the Surgeon General's Report on physical activity and health status which states that 'regular physical activity appears to improve HRQoL by enhancing psychological well-being and by improving physical functioning in persons comprised by poor health'.[21] Although different aspects of everyday physical activity were measured, Painter et al. also found that physical activity is related to HRQoL after liver transplantation. [22] They measured participation in regular physical activity in 180 persons five years or more after liver transplantation; for this purpose a questionnaire was used with specific questions about type, frequency, duration, and intensity of exercise participation. Liver transplant recipients who participated in regular physical activity had significantly higher scores on all physical domains of the SF-36 than inactive liver recipients. Painter et al. found no significant differences for the mental domains, which is in contrast with the results of the present study.

In conclusion, five of the eight liver transplant recipients were classified as hypoactive, but as a group, the liver transplant recipients were not significantly less active than their comparison subjects. Severity of fatigue in the liver transplant recipients was related to the level of everyday physical activity. Furthermore, activity levels were related with HRQoL. No indications were found that levels of everyday physical activity in liver transplant recipients improve over time. These findings have implications for the development of interventions needed to rehabilitate persons after liver transplantation.

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Chapter 6

Physical rehabilitation after liver transplantation improves fatigue and fitness

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Submitted

Abstract

Objective Fatigue is a chronic problem following liver transplantation that may be related to low levels of physical fitness and daily physical activity. This study aimed to evaluate the feasibility and effects of a rehabilitation program designed to improve physical fitness and daily physical activity, on fatigue in liver transplant recipients.

Design Uncontrolled intervention study.

Methods Eighteen fatigued liver transplant recipients participated in a 12-week rehabilitation program, which included supervised exercise training and counseling about daily physical activity. We assessed pre- and post-program fatigue, aerobic capacity, muscle strength, body fat, daily physical activity, cholesterol ratios and glycemic control. We also assessed fatigue at one year after finishing the program.

Results Attendance (93%) and mean patient satisfaction (8.5 out of 10) were high. Post-program, patients were less fatigued (12.2-21.6%, $p < .05$), and had improved aerobic capacity (6.4%, $p = .01$) and muscle strength (4.8-16.4%, $p < .05$). Daily physical activity, cholesterol ratios and glycemic control did not change. Fatigue scores at one-year follow-up did not significantly differ from pre-program scores.

Discussion Rehabilitation using supervised exercise training and daily physical activity counseling is feasible and effective in decreasing fatigue and improving fitness among liver transplant recipients. However, the program demonstrated no long-term benefits on fatigue.

Introduction

Over the past few decades, liver transplantation (LTx) has been associated with increased one- and five-year survival, increased graft survival, and reduced rejection episodes.[1] Recently, researchers have shifted focus to prevent long-term complications and improve health-related quality of life (HRQoL). Most studies show that patients enjoy improved HRQoL following LTx, but that HRQoL does not reach that of the healthy population.[2, 3] Fatigue is a major problem following LTx.[4-7] In a previous longitudinal study of LTx recipients, we found a high prevalence of fatigue (20%) and severe fatigue (40%), which did not decrease over time.[7] These findings suggest that, in the absence of intervention, fatigue is a chronic and important problem following LTx.

We previously reported that low daily physical activity (PA) levels and poor physical fitness may be associated with fatigue after LTx.[8, 9] Although the small sample size and cross-sectional design did not allow a determination of causality, we hypothesized that LTx recipients experience a cycle of fatigue leading to inactivity, which leads to a reduction in physical fitness, which in turn leads to more fatigue.

A rehabilitation program designed to enhance physical fitness and daily PA may help reduce fatigue after LTx by breaking this cycle of fatigue, inactivity, and deconditioning. Physical exercise programs are widely reported to favorably impact fatigue in healthy persons and those with other chronic illnesses.[10-14] Rehabilitation including exercise training may improve physical fitness (aerobic capacity, muscle strength, and body composition) while reducing cardiovascular disease risk.[9, 15-19]

Customary medical care following LTx focuses on prevention of graft rejection, immunosuppressant management, dietary counseling, and psychosocial support. Therapeutic exercise training is seldomly included in LTx rehabilitation programs, and exercise training studies are limited in this population.[15, 20, 21] To the best of our knowledge, there have been no studies examining the effect of rehabilitation on fatigue in long-term LTx recipients. Because (severe) fatigue is highly prevalent in LTx recipients, it is important to determine whether an intensive physical rehabilitation program is feasible and effective for this patient group.

This study aimed to determine feasibility and effect of a supervised exercise training program and PA counseling for LTx recipients. The study aimed to examine the effects of the program on fatigue, physical fitness, daily PA, and cardiovascular disease risk.

Methods

Subjects

Patients were recruited from outpatient LTx recipients at the Erasmus University Medical Center. We selected patients who were (a) fatigued (defined as a Fatigue Severity Scale (FSS) score ≥ 4[6]), (b) aged between 18 and 65 years, and (c) transplanted at least one year prior to study initiation. Patients were excluded for (a) multi-organ transplant, (b) severe co-morbidity (e.g. recurrent cholangitis or cancer), (c) insufficient knowledge of the Dutch language, or (d) contra-indication to exercise or progressive maximal cycle ergometer test (e.g. cardiovascular disease).

Eligible patients received patient information handouts. The Medical Ethics Committee of the Erasmus University Medical Center Rotterdam approved the study. Written informed consent was obtained from all subjects.

Design

We conducted an uncontrolled intervention study, because this study was the first step to test the feasibility of an intensive physical rehabilitation program (supervised training twice weekly) among fatigued LTx recipients, and to study possible effects on fatigue, physical fitness (aerobic capacity, muscle strength, and body composition), daily PA, and cardiovascular disease risk. Eligible patients completed the FSS questionnaire[22] prior to program initiation. Measurements were conducted one week before and one week after a 12-week rehabilitation program. On the day of the measurements, patients refrained from caffeine, nicotine, and heavy exercise. Patients completed a 6-minute walk test (6MWT[23]), followed by body composition measurements and biochemical profile measurements (cardiovascular risk), strength tests, and a progressive maximal cycle ergometer test. Patients performed exercise tests under physician supervision. Patients rested for 30 minutes between tests. Daily PA measurements were performed during two randomly selected, consecutive weekdays in patients' homes. One year after the program, we asked patients to complete fatigue questionnaires to evaluate the long-term effects on fatigue (follow-up measurement).

Program

The 12-week rehabilitation program included (a) supervised one-hour exercise training sessions (aerobic and strength training) twice weekly, and (b) four daily activity behaviour counseling sessions, conducted during weeks one, four, eight, and twelve. Exercise training sessions were conducted in groups of two to four patients, and counseling sessions were performed individually. All training and counseling sessions were conducted by a physical therapist at the Department of Rehabilitation at Erasmus University Medical Center.

Aerobic training consisted of 30-minute ergometer cycling starting at a heart rate reserve (HRR) intensity of 40 to 50% and increasing to 70 to 80% using the Karvonen method.[24] We aimed for a mean target intensity of 60% of HRR over the 12-week program, in accordance with American College of Sports Medicine (ACSM) guidelines.[25]

Strength training included 30 minutes targeted to major muscle groups (i.e. quadriceps femoris, biceps brachii, gluteus maximus, gluteus medius, and abdominal muscles). Over the 12-week period, the intensity and number of repetitions were gradually increased from 1 set of 10 to 15 repetitions at 30% of the one-repetition maximum (1RM), to 3 sets of 20 repetitions at 60% of the 1RM (moderate intensity).[25] After each training session, patients indicated the strenuousness of their training from 0 (no effort at all) to 10 (maximal effort), using the Borg Category Scale for Rating of Perceived Exertion.[26]

The purpose of daily activity behaviour counseling sessions was to stimulate increased daily PA among patients, and is based on Van der Ploeg et al.'s 'Active after Rehabilitation' program that was developed by EMGO Institute VU Medical Center (Amsterdam, The Netherlands) and HealthPartners Health Behaviour Group (Minneapolis, USA).[27] This program is based on the Transtheoretical model stages of change: pre-contemplation (not intending changing lifestyle in the next six months), contemplation (intending changing lifestyle in the next six months), preparation (intending changing lifestyle within a month and have taken some action in the past year), action (having made specific overt modifications in lifestyle within the past six months), and maintenance (continuing lifestyle change and preventing relapse).[28] During counseling sessions, patients received information about activities, sports, and

health, and also facilitators, barriers, and PA possibilities were discussed. Sessions were supported by written materials specific to patients' stage of PA change (EMGO Institute VU Medical Center and HealthPartners Health Behaviour Group). Patients who moved between stages received new information specific to their stage.

Measurements

Feasibility

To study program feasibility we recorded: (a) the proportion of patients who were ineligible due to exclusion criteria, (b) the willingness of eligible patients to participate, (c) the proportion of patients that dropped out of the study and reasons for drop-out, (d) the proportion of sessions attended and reasons for missed sessions, (e) the achieved training intensity, (f) participants' satisfaction with the program rated on a 10-point scale (a higher score indicates higher satisfaction), and (g) adverse events. We defined adverse events as any injuries or events that occurred during testing or training (musculoskeletal or cardio-respiratory).

Fatigue severity

We assessed fatigue severity by: (a) the FSS, a validated nine-item questionnaire with scores ranging from 1 to 7[22, 29]; (b) a horizontal visual analog scale (VAS); and (c) the fatigue severity subscale of the Checklist Individual Strength (CIS-fatigue). We defined 'fatigue' as an FSS score of 4.0 to 5.1 and 'severe fatigue' as an FSS score of greater than or equal to 5.1.[6] For the VAS, a validated and reliable scale[30, 31], we asked patients to mark a 100-mm line according to the intensity of fatigue experienced during the last month (0 indicates 'no fatigue experienced' and 100 indicates 'the most severe fatigue').[32] The subscale CIS-fatigue consists of eight items with scores ranging from 8 to 56, with higher scores indicating greater fatigue.[33] The CIS-fatigue has good reliability, validity, and sensitivity.[34, 35]

Physical fitness: Aerobic capacity

Aerobic capacity was measured with a progressive maximal aerobic test on a cycle ergometer (ER800, Jaeger Toennies, Breda, The Netherlands). We measured gas exchange and heart rate continuously using a breath-by-breath gas analysis system (K4b2, COSMED, Rome, Italy). We defined aerobic capacity as the mean oxygen uptake during the final 30 seconds of exercise (VO_{2peak}, in $ml \cdot min^{-1}$ and in $ml \cdot kg^{-1} \cdot min^{-1}$). We also recorded the distance walked during the 6MWT (6MWD).[23] On the day prior to pre and post tests, we checked hemoglobin concentrations (Hb) to standardize physical fitness measurements because hemoglobin levels may vary due to renal insufficiency or immunosuppressants such as tacrolimus and cyclosporine.[36]

Physical fitness: Muscle strength

We assessed isokinetic knee extensor (quadriceps) and knee flexor (hamstrings) strength with a Biodex® dynamometer (Shirley, New York, USA), recording strength as torque in Newton meters (Nm). Isokinetic strength was measured at 60°/s with five maximal contractions. Peak torque (PT) was defined as the maximum torque generated during one series of repetitions.

Physical fitness: Body composition

Body mass was measured using a Cormier Paribel® weighing chair (FH Balances Cormier, Romainville, France). Body mass index (BMI, $kg \cdot m^{-2}$) was calculated from height and body mass. Four skinfold thickness measures (biceps, triceps, subscapular region, and suprailiac region) were made twice on the right side of the body with a Harpenden Skinfold Caliper (Burgess Hill, United Kingdom). The mean of two measurements was used as representative for each site. Percentage body fat was predicted from skinfold thickness according to the method of Durnin and Womersley.[37]

Daily physical activity

We assessed daily PA using an activity monitor (AM, Temec Instruments, Kerkrade, The Netherlands), which conducts long-term ambulatory monitoring of signals from body-fixed accelerometers. The AM determines duration, rate, and moment

of occurrence of postures (lying, sitting, and standing) and activities (walking, stair-climbing, running, cycling, wheelchair-driving, and general non-cyclic movement). Furthermore, variability of acceleration signal (motility) can be obtained by measuring intensity of body segment movements. The AM is valid to quantify mobility-related activities.[38]

We measured AM on two randomly selected consecutive weekdays (48-hour measurement). Data from AM measurement were calculated per day and, because there were no intra-day differences, averaged over two days. We assessed duration of dynamic activities as percentages of 24-hour periods. In addition, we assessed body motility using mean motility (representing intensity and duration of daily PA) and motility during walking (representing walking speed). To avoid measurement bias, we explained the principles of the AM to subjects after measurements were made. Subjects were instructed to continue their ordinary routines except for swimming, bathing, and showering during the AM measurement period.

We also assessed perceived daily PA using the 7-day recall Physical Activity Scale for Individuals with Physical Disabilities (PASIPD), which identifies leisure time, household activities, and work-related physical activities.[39] The PASIPD has a test-retest reliability and criterion validity comparable to well-established, self-report physical activity questionnaires from the general population.[40]

Cardiovascular risk

We determined cardiovascular risk by assessing lipid profiles and glycemic control. Non-fasting venous blood samples were obtained while patients were seated. Routine hematologic and biochemical analyses were performed in the hospital laboratory using a Roche Modular P system (Basel, Swiss) and a Bayer DCA2000 (Leverkusen, Germany). To study the effects on lipid profiles, we assessed the ratio of total cholesterol to high-density lipoprotein cholesterol (TC/HDL-C ratio) and the ratio of low-density lipoprotein cholesterol to HDL-C (LDL-C/HDL-C ratio). To assess glycemic control, we measured glycosylated hemoglobin (HbA1c).

Statistical analysis

We used SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) for statistical analyses. Aspects of feasibility were analyzed descriptively and reported as means with standard deviations (SD). We compared fatigue severity, aerobic fitness, muscle strength, body composition, daily PA, and biochemical profiles before and after the rehabilitation program using the non-parametric Wilcoxon Matched-Pairs Signed-Ranks Test. A probability of $p \leq .05$ was used to determine statistical significance. Because of the relatively small study sample, we also report results at the $\alpha = .10$ level to show non-significant trends. We compared fatigue severity at follow-up with pre- and post-program fatigue scores using non-parametric Wilcoxon Matched-Pairs Signed-Ranks Tests and corrected for multiple testing. For the follow-up analysis of the FSS score, a probability value $\leq .025$ was used to determine statistical significance.

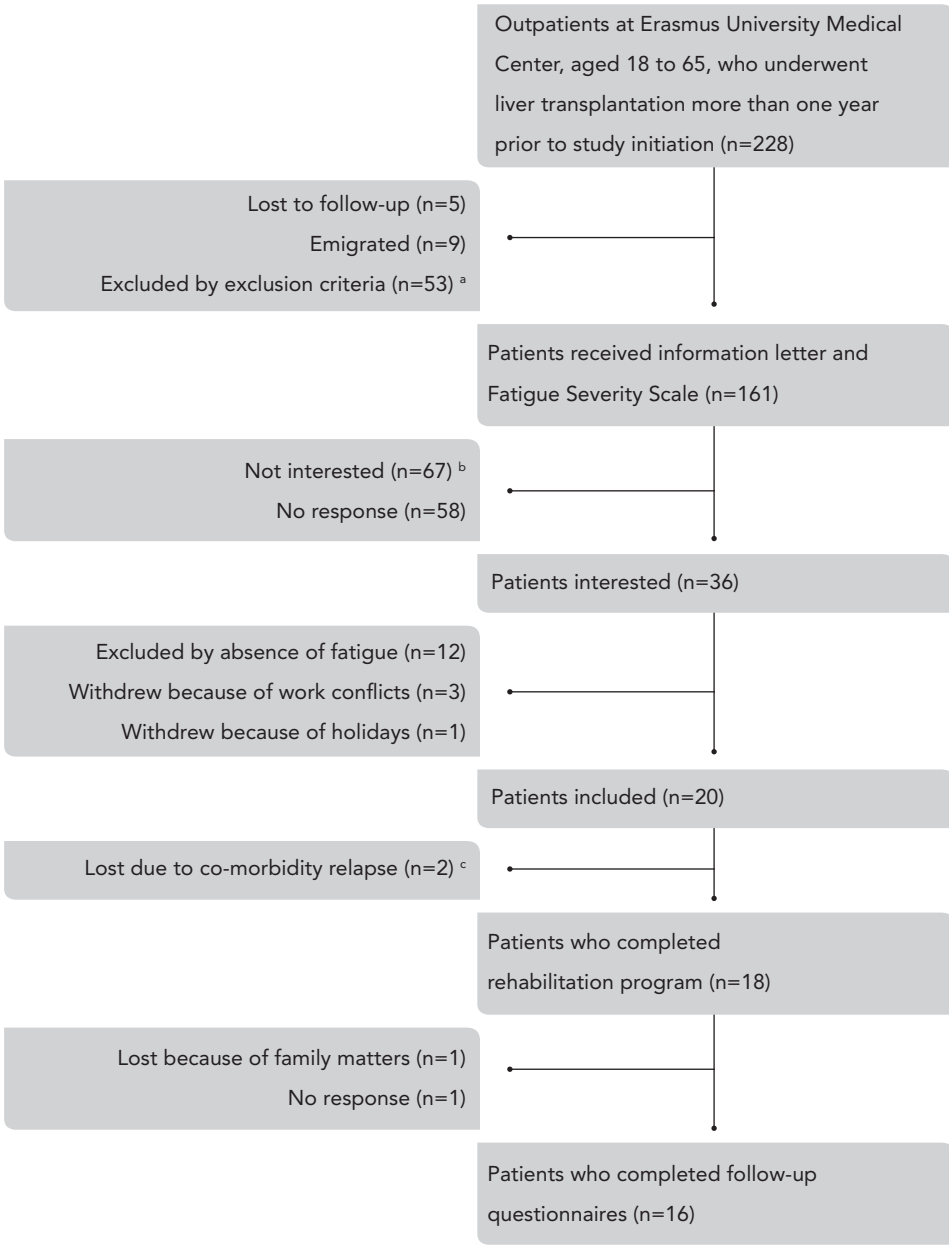
Results

Patients and feasibility

Figure 1 shows the flow of participants through the study. A total of 18 patients completed the study and 16 patients completed questionnaires at one-year follow-up. Patients' characteristics are presented in Table 1. Patients' pharmacologic regimens remained stable during the program, except for one patient whose anti-hypertensives were reduced two weeks after study initiation.

On average, the patients attended 93% (range 75% to 100%) of training sessions. The primary reason for missed sessions was fatigue. The mean training intensity over the 12 weeks was 60.0% ± 7.7%, with an average perceived exertion of 4.1 ('somewhat strenuous'). Four patients achieved the target intensity of 70% to 80% HRR during the last four training sessions. During the tenth week, we reduced the training intensity for one patient who complained of musculoskeletal pain. The mean intensity of the strength training was 51% of the 1RM. No training-related injuries or adverse events occurred. The patient mean satisfaction score was 8.5 out of 10 (range 7 to 10).

Figure 1. Flow-chart of the study



[a] Excluded, because of various co-morbidities and/or contra-indications for exercise or maximal exercise test
[b] Not interested, because of: distance (n=17), lack of time (n=11), fatigue (n=10), no reason (n=29)
[c] Lost, because of: relapse of psychological problems (n=1), relapse of intestinal disorder (n=1)

Table 1. Patient characteristics (n=18)

Age (years)	51.0 (33.9 - 62.5)
Sex (n)	
Men	10
Women	8
Height (m)	1.74 (1.63 - 1.89)
Mass (kg)	91.1 (60.2 - 129.0)
Time since transplantation (years)	7.5 (1.3 - 17.0)
Primary disease (n) [a]	
Chronic	13
Acute	5
Number of immunosuppressive agents (n) [b]	
1	13
2	3
3	2
Liver Function [c]	
ALT (U/l)	32.1 (0.4)
AST (U/l)	30.7 (6.6)
GGT (U/l	90.7 (122.3)
TBIL (umol/l)	12.1 (6.9)

Results are presented as mean (range) or number of patients

[a] Chronic primary disease: viral (n=3), cholestatic (n=3), auto immune cirrhosis (n=1), cryptogenic cirrhosis (n=4), Wilson's disease (n=1), polycystic liver disease (n=1); Acute primary disease: viral (n=1), acute liver failure e causa ignota (n=2), auto immune hepatitis (n=1), Wilson's disease (n=1)

[b] Immunosuppressive agents: 1 agent, tacrolimus (n=8), cyclosporine (n=3), mycophenolate (n=1) or everolimus (n=1); 2 agents, prednisone with tacrolimus (n=2) or prednisone with cyclosporine (n=1); 3 agents, prednisone with tacrolimus and azathioprine (n=1) or prednisone with cyclosporine and mycophenolate (n=1)

[c] Liver function: ALT, alanine transaminase (n=15); AST, aspartate transaminase (n=15); GGT, gamma glutamyl transpeptidase (n=15); TBIL, total bilirubin (n=15)

Changes in fatigue, physical fitness, biochemical profile, and daily physical activity

After the program, mean fatigue was significantly reduced by 12.2% to 21.6% ($p < .05$) (Table 2). Of 18 patients, 10 were severely fatigued (FSS ≥ 5.1) at baseline. Two patients severely fatigued (FSS ≥ 5.1) at baseline were classified as fatigued (4.0 ≤ FSS < 5.1), and one as non-fatigued (FSS < 4.0) at program conclusion. Four of the eight fatigued patients became non-fatigued after the program. One fatigued patient became severely fatigued after the program (Table 3).

Aerobic capacity improved by 5.4% to 7.8% ($p < .05$) (Table 2). There were no differences in hemoglobin between baseline and program conclusion. Muscle strength increased after the program, but only the absolute PT of knee flexion reached significance ($p = .041$). At program initiation, ten of 18 patients were obese (BMI > 30). At program conclusion, BMI was unchanged; however, body fat percentage decreased significantly. There were no significant differences in duration of dynamic activities, mean motility, motility during walking, or perceived daily PA. There were no differences in cholesterol ratios or glycemic control (Table 4).

Fatigue at one-year follow-up

Figure 2 shows FSS, VAS and CIS-fatigue results for 16 participants at baseline, program conclusion, and one-year follow-up. One-year FSS scores did not differ from post-program FSS scores ($p = .50$). One-year VAS and CIS-fatigue scores increased (deterioration) compared to post-program scores ($p = .09$ and $p = .01$, respectively). One-year FSS, VAS, and CIS-fatigue scores did not significantly differ from pre-program scores ($p = .14$, $p = .68$, and $p = .96$, respectively).

Table 2. Fatigue, physical fitness and daily physical activity before and after the 12-week rehabilitation program (n=18)

	Before intervention	After intervention	Change	p-value
Fatigue severity				
FSS	5.3 (0.9)	4.7 (1.3)	-12.2%	.014*
VAS	63.0 (20.1)	49.4 (22.6)	-21.6%	.043*
CIS-fatigue	37.2 (10.0)	29.8 (9.4)	-19.9%	.007*
Aerobic capacity				
Peak oxygen uptake (mL/min)	1936.0 (589.3)	2060.5 (624.5)	6.4%	.012*
Peak oxygen uptake (mL/kg/min)	21.9 (7.1)	23.2 (7.1)	5.9%	.031*
Load (W)	143 (51)	154 (53)	7.8%	.003*
Load (W/kg)	1.62 (0.61)	1.74 (0.63)	7.4%	.004*
6-minute walking distance (m)	544.9 (72.2)	574.4 (68.9)	5.4%	.004*
Muscle strength				
Peak torque knee extension (Nm)	131.5 (47.3)	138.9 (48.7)	5.7%	.094†
Peak torque knee extension (Nm/kg)	1.47 (0.48)	1.55 (0.48)	5.5%	.058†
Peak torque knee flexion (Nm)	60.3 (26.3)	66.6 (29.4)	10.4%	.041*
Peak torque knee flexion (Nm/kg)	0.67 (0.29)	0.74 (0.31)	10.4%	.058†
Body Composition				
Body mass index	30.1 (5.6)	30.1 (5.7)	0.2%	.287
Body fat (%)	34.2 (7.3)	33.4 (7.1)	-2.2%	.049*
Daily activity				
Duration of dynamic activities (%)	10.3 (5.2)	9.6 (5.1)	-7.6%	.948
Mean motility (g) [a]	0.026 (0.015)	0.024 (0.013)	-8.2%	.845
Motility during walking (g) [b]	0.176 (0.061)	1.172 (0.060)	-2.6%	.500
PASIPD (MET-hr/day)	15.5 (8.9)	16.6 (9.1)	6.8%	.248

Results are presented as mean (SD)

[a] Intensity of daily activity (1 g = 9.81 $m \cdot s^2$)

[b] Walking speed

FSS: Fatigue Severity Scale[21]

VAS: Visual Analogue Scale[31]

CIS-fatigue: fatigue severity subscale of the Checklist Individual Strength[32]

PASIPD: Physical Activity Scale for Individuals with Physical Disabilities[37]]

* Significant ($p \leq .05$) difference

† Difference at the $\alpha = .10$ level (trend)

Table 3. Fatigue before and after the 12-week rehabilitation program (n=18)

	n
Severe fatigue before the intervention (FSS score ≥ 5.1)	**10**
severe fatigue at follow-up	7
fatigue at follow-up	2
no fatigue at follow-up	1
Fatigue before the intervention (4.0 ≤ FSS score < 5.1)	**8**
severe fatigue at follow-up	1
fatigue at follow-up	3
no fatigue at follow-up	4

FSS: Fatigue Severity Scale[21]

Table 4. Biochemical markers before and after the 12-week rehabilitation program (n=18)

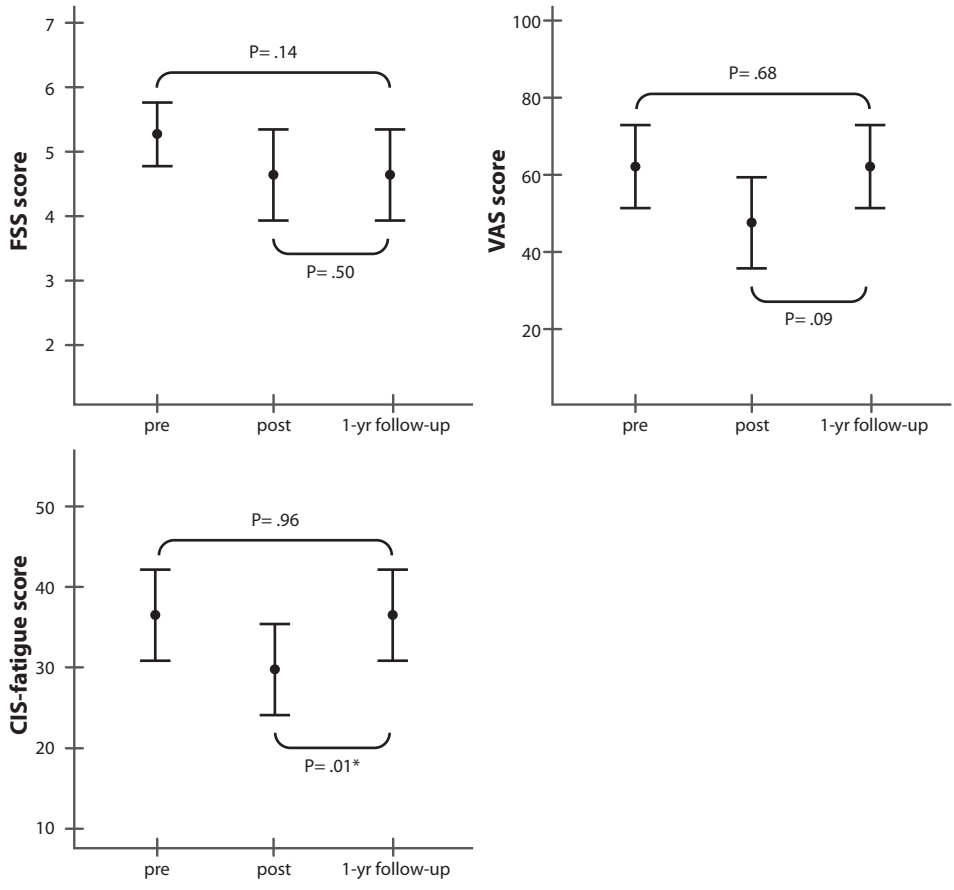
	Before intervention	After intervention	p-value
Cholesterol ratios			
TC/HDL-C ratio	4.2 (1.7)	4.2 (1.6)	.538
LDL-C/HDL-C ratio	2.4 (1.1)	2.4 (1.1)	.831
Glycemic control			
HbA1c (%)	5.6 (1.6)	5.7 (1.3)	.071†

Results are presented as mean (SD)
TC/HDL-C ratio, total serum cholesterol/high-density lipoprotein cholesterol ratio (n=16)
LDL-C/HDL-C ratio, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio (n=17)
HbA1c, glycosylated hemoglobin (n=12)
† Difference at the α= .10 level (trend)

Discussion

To our knowledge, this is the first study to evaluate the effects of a rehabilitation program on fatigue in LTx recipients. It appears that a 12-week supervised exercise training program in combination with activity counseling is feasible and effective in reducing fatigue, and improving aerobic capacity, muscle strength, and body fat in fatigued LTx recipients. However, the results indicate that the decrease in fatigue did not persist at one year.

Figure 2. Fatigue before and after the program, and at one-year follow-up (n=16)



* Significant (p≤ .025) difference

Feasibility

Our results show the feasibility of a 12-week rehabilitation program for fatigued LTx recipients that included exercise training and daily PA counseling. However, it is difficult to extrapolate results to larger LTx patient populations because of the large proportion of patients excluded from the study due to co-morbidities or contra-indications. Although participants achieved the suggested mean training intensity of 60% HRR, non of the patients could achieve the high intensity training goal of 70% to 80% of HRR.

In general, participants were very satisfied with the program and mean attendance was high. Participants mentioned long travel distance to the training location as a barrier to participation. Future training sites should be more conveniently located near participants' homes to allow more training sessions per week and possibly increase the training effect.

Changes in fatigue

The 12% to 22% improvement in fatigue scores at program conclusion is consistent with other studies of fatigued patients that used the FSS, VAS, and CIS-fatigue questionnaires.[41, 42] This level of improvement is considered clinically relevant.[43-45] Although fatigue reductions were not sustained at one-year follow-up, the three fatigue scales showed differing patterns. One-year FSS scores did not differ from post-program FSS scores, although one-year VAS and CIS-fatigue scores worsened compared to post-program scores. The FSS may be less sensitive to change than the other fatigue questionnaires. Overall, the program demonstrated no long-term benefits on fatigue. Future studies must focus on developing and testing fatigue-reducing interventions with sustained long-term effects.

Future research with larger study samples is needed to determine the mechanism of the decreased fatigue, and to confirm our hypothesis that enhanced physical fitness and daily PA help break the cycle of inactivity, deconditioning, and fatigue in LTx recipients. Also other factors may have been responsible for the post-program reduction of fatigue, including the influence of group training on social support, refocusing of attention, and the influence of exercise on patients' feelings of control or decrease in focus on symptoms.[13, 14] Over the long-term, these factors may become less important, leading patients to experience increased sensations of fatigue. Studies have shown that cognitive behaviour therapy (CBT) is effective in treating fatigue in various patient groups.[46, 47] CBT is a general form of psychotherapy, and incorporates elements of both behavioural therapy (BT) and cognitive therapy approaches.[46] Gielissen et al. showed that the positive effects of CBT on fatigue in cancer survivors remained after four years.[47] However, studies of the long-term effects of CBT on fatigue are scarce and inconsistent.[46] Future research is needed to investigate CBT as a possible treatment for fatigue in LTx recipients.

Changes in physical fitness

The 6.4% mean increase in VO_{2peak} is low compared to expected aerobic improvements of 5% to 25% following systematic endurance training programs.[48] We expected larger improvements in aerobic capacity, especially given our patients' low baseline measures (30% lower aerobic capacity compared to age and sex-matched healthy subjects as measured in our research lab). However, 12-week training studies in heart failure and cancer survivors also showed relatively small VO_{2peak} improvements of 7% to 10%.[49-52] Improvements of sub-maximal 6MWD, which is physiologically similar to daily activity, are somewhat lower compared with other study findings.[53] The relatively small improvements in VO_{2peak} and 6MWD may be explained by the low number of weekly training sessions. Because of fatigue, work conflicts, and long distances to the training site, patient training sessions were reduced to two times per week instead of the recommended three times per week.[25]

As in previous training studies, we found an improvement in knee muscle strength after the 12-week program.[54, 55] However, these improvements were only significant for the absolute PT of knee flexion. Again, the relatively small improvements in muscle strength may be explained by reduced number of weekly training sessions. As with aerobic capacity, we expected larger improvements in muscle strength because of low pre-program fitness levels (26% lower muscle strength compared to age and sex-matched healthy subjects as measured in our research lab). To attain larger training effects in future programs, additional home-based strength exercises should be considered.

Although we found a small but significant decrease in body fat, we did not observe decreases in BMIs. This finding has also been seen in other studies, and may be explained by increases in lean body mass.[56, 57] Therefore, BMI may not be a good effect parameter for training intervention studies.

Changes in daily physical activity

The 12-week rehabilitation program was not effective in improving daily PA in fatigued LTx recipients. Patients indicated that the 12-week program was very intensive. The training visits may have placed additional burdens on patients that negatively impacted efforts of patients to further increase daily PA levels.

Furthermore, the lack of change in daily PA may be explained by the observation that patients' mean pre-program dynamic activity durations (10.3%) were similar to those of age and sex-matched healthy subjects (11.7%). It is remarkable that these patients had normal PA levels despite their fatigue. We could speculate that the LTx recipients were fatigued because they are too active with regard to their physical fitness and overburden themselves. However, results of our previous study showed that a lower PA level is associated with more fatigue[8], and also the present results do not support this possible explanation.

Changes in biochemical profile

We did not observe any changes in cholesterol ratios or glycemic control after the program. In contrast, several studies in patients with type 2 diabetes have shown that exercise training reduces HBA1c.[58-60] Because HbA1c in our patients was somewhat high, we would have expected HbA1c to decrease. It is possible that the period (i.e. one week) between program conclusion and biochemical profile measurements was too short to detect any effects of the program on lipid and glucose measures.

Limitations

The major limitation of this study is the lack of a control group. However, this intervention study was the first step to test the feasibility of a rehabilitation program in fatigued LTx recipients, and to study possible effects on fatigue. Although our previous study showed that, without intervention, fatigue is a persistent problem after LTx, a randomized controlled trial is needed to draw stronger conclusions about the effect of rehabilitation on fatigue. Another limitation is possible selection bias at time of patient recruitment. Participants are likely to be highly motivated, as illustrated by their willingness to attend two exercise sessions per week for 12 weeks at our rehabilitation department. Furthermore, participants may not be representative of the study population because they had no contra-indications for exercise or the maximal ergometer test. Also, the small study sample and the large number of excluded patients make it difficult to generalize findings to all LTx recipients.

In conclusion, we have shown that a 12-week rehabilitation program, consisting of supervised exercise training and PA counseling, is feasible and effective in decreasing fatigue in LTx recipients shortly after the program. The program was also effective

in improving physical fitness, but had no effect on daily PA. Moreover, the program demonstrated no long-term benefits on fatigue. Future research with larger study samples is needed to determine the mechanism of the decreased fatigue and to develop long-term fatigue-reducing interventions for LTx recipients.

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Chapter 7

Benefits of a rehabilitation program on daily functioning, participation and quality of life in liver transplant recipients

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Submitted

Abstract

Objective Fatigue is a chronic problem in liver transplant recipients, and is related to daily functioning and health-related quality of life. This study aimed to evaluate the effects of a fatigue-reducing physical rehabilitation program on daily functioning, participation, and health-related quality of life among liver transplant recipients.

Design Uncontrolled intervention study.

Methods Eighteen fatigued liver transplant recipients participated in a 12-week rehabilitation program, which included supervised exercise training and daily physical activity counseling. We assessed pre- and post-program health-related daily functioning, participation, and health-related quality of life.

Results After the program, patients showed improvements in daily functioning (23.6%, p= .007), the participation domain 'autonomy outdoors' (34.1%, p= .001), and the health-related quality of life domains 'physical functioning' (11.5%, p= .007) and 'vitality' (21.5%, p= .022).

Discussion Rehabilitation using supervised exercise training and daily physical activity counseling can positively influence daily functioning, participation, and health-related quality of life among liver transplant recipients.

Introduction

Liver transplantation (LTx) is the treatment of choice for end-stage liver disease, and is associated with excellent mid-term and long-term outcomes.[1] As a result, there is now increased attention on improving the transplant recipient's quality of life.[2, 3] Most studies on health-related quality of life (HRQoL) after LTx report that HRQoL improves markedly after LTx.[3] However, recipients show considerable deficits in most HRQoL domains, with the notable exceptions of 'mental health' and 'bodily pain'. According to several studies, fatigue is a major problem after LTx.[4-7] In a previous longitudinal study, we found that 60% of LTx recipients reported fatigue or severe fatigue which did not decrease over time.[6, 7] The exact cause of this fatigue is unknown. Previous work in LTx recipients has established that fatigue after LTx may be associated with low levels of daily physical activity and poor physical fitness.[8, 9]

Several studies in non-transplant patients have shown that exercise training favorably impacts HRQoL[10-13], especially for the 'physical domains'.[10] Endorphins, distraction, positive feedback, and social interaction are thought to be involved in this improvement.[13] Moreover, an active lifestyle appears to improve HRQoL in patients with poor health by enhancing psychological well-being and improving physical functioning.[14]

Krasnoff et al.[15] showed that, within the first year after LTx, patients engaging in a ten-month home-based exercise training program experienced improvements in the HRQoL domain 'general health'. However, there have been no studies on the effects of a physical rehabilitation program on health-related daily functioning, participation, and HRQoL in long-term LTx recipients. We previously demonstrated that 12 weeks of exercise training plus daily activity counseling decreased fatigue (12.2% to 21.6%), and improved both aerobic capacity (6.4%) and muscle strength (4.8% to 16.4%) in fatigued patients who were at least one year post-transplant (Chapter 6). Because we previously showed that fatigue after LTx negatively affects patients' health-related daily functioning and HRQoL[7], we aimed to study whether this fatigue-reducing 12-week exercise training program plus daily activity counseling is also beneficial in improving health-related daily functioning, participation, and HRQoL.

Methods

Subjects

We recruited outpatient LTx recipients at the Erasmus University Medical Center, who were (1) fatigued (defined as a Fatigue Severity Scale score ≥ 4[16]), (2) aged 18 to 65 years, and (3) transplanted at least one year prior to study initiation. Patients were excluded for (1) multi-organ transplant, (2) severe co-morbidity (e.g. recurrent cholangitis or cancer), (3) insufficient knowledge of the Dutch language, or (4) contraindication to exercise or progressive maximal cycle ergometer test (e.g. cardiovascular disease). We obtained data on patient age, sex, cause of liver disease, type and number of immunosuppressants, home situation, employment, and sports. The Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety symptoms.[17, 18] The Medical Ethics Committee of the Erasmus University Medical Center Rotterdam approved the study. Written informed consent was obtained from all subjects.

Design

We performed an uncontrolled intervention study, because this was the first study to assess such an intensive physical rehabilitation program (supervised training twice weekly) among fatigued LTx patients. Patients were asked to complete questionnaires on health-related daily functioning, participation, and HRQoL. Patients completed questionnaires under researcher supervision at the Department of Rehabilitation Medicine of the Erasmus University Medical Center one week before and one week after the 12-week rehabilitation program.

Program

The 12-week rehabilitation program included (1) supervised, twice weekly, one-hour exercise training sessions (aerobic and strength training), and (2) four daily activity counseling sessions, conducted at weeks one, four, eight, and twelve. The purpose of the daily activity behaviour counseling was to stimulate increased physical activity among patients, and is based on the 'Active after Rehabilitation' program that was developed by EMGO Institute VU Medical Center (Amsterdam, The Netherlands)

and HealthPartners Health Behaviour Group (Minneapolis, MN, USA).[19] Exercise training sessions were conducted in groups of two to four patients, and counseling sessions were performed individually. All training and counseling sessions were conducted by a physical therapist at the Department of Rehabilitation at Erasmus University Medical Center.

Outcome measures

Health-related daily functioning

We assessed health-related daily functioning using the validated self-assessment version of the Sickness Impact Profile-68 (SIP-68). The SIP-68 assesses the impact of illness on health-related daily functioning and behaviour. It includes six scales to assess the effect of health on (1) somatic functions (e.g. standing, walking, eating, dressing), (2) control of body movements (e.g. walking, arm functions, and hand functions), (3) mental functioning and communication abilities (e.g. attention problems), (4) social functioning (e.g. sexual activities, visiting friends), (5) emotional stability (e.g. irritability), and (6) mobility range (e.g. shopping, house cleaning, conducting personal business).[20, 21] The total score ranges from 0 to 68, with higher scores indicating a lower level of health-related daily functioning. The SIP-68 is used extensively in studies of LTx recipients.[6, 22-24]

Participation

We assessed restriction in participation and autonomy using the Impact on Participation and Autonomy (IPA) scale.[25, 26] The IPA assesses participation using 32 items across five domains that address different life situations. The participation domain 'autonomy indoors' measures the ability to care for one's self as desired. The domain 'family role' measures the ability to fulfill one's role in the home. The domain 'autonomy outdoors' measures the ability to pass leisure time and visit friends as desired. The domain 'social relations' measures the ability to interact with the environment, participate in a balanced conversation or be intimate. The domain 'job and education' measures the ability to work and find employment or education according to one's wishes. Participation is graded on a five-point scale

ranging from very good (0) to very poor (4). For each domain, the participation score is calculated by summing the item scores. Higher scores indicate more restrictions in participation. The scale shows good reliability and validity.[25, 26]

Health-related quality of life

We assessed HRQoL using the validated Dutch version of the Medical Outcomes Study Short Form-36, the RAND-36 Health Survey (RAND-36).[27] The RAND-36 is a self-administered questionnaire used internationally to measure self-perceived health status in the domains of 'physical functioning' (perceived limitations in performing physical activities), 'social functioning' (perceived limitations in performing social activities), 'role limitations due to physical problems' (perceived problems with work or other daily activities because of physical problems), 'role limitations due to emotional problems' (perceived problems with work or other daily activities because of emotional problems), 'pain' (perceived pain), 'mental health' (feelings of nervousness and depression), 'vitality' (perceived fatigue or energy), 'general health perception' (evaluation of personal health and expectations of changes in health), and 'change in health' (perceived change in general health status over a one-year period).[28] We converted all raw scores to a 100-point scale, with higher scores indicating higher levels of HRQoL.

Statistical analysis

We used SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) for statistical analyses. We compared health-related daily functioning, participation, and HRQoL before and after the rehabilitation program using the non-parametric Wilcoxon Matched-Pairs Signed-Ranks Test. A probability of $p \leq .05$ was used to determine statistical significance. Because of the relatively small study sample, we also reported results at the $\alpha = .10$ level to show non-significant trends.

Results

Patients

Figure 1 of Chapter 6 shows the flow of participants through the study. Patients' baseline characteristics are shown in Table 1. At baseline, four patients had elevated depression scores (HADS-D ≥ 8) and three patients had elevated anxiety scores (HADS-A ≥ 8) (Table 1).[18]

Changes in health-related daily functioning, participation, and HRQoL

Table 2 shows the effects of the 12-week rehabilitation program on daily functioning, participation, and HRQoL. Health-related daily functioning, as measured by the SIP-68, improved significantly over the course of the study (-23.6%; p= .007). The IPA-measured participation domain of 'autonomy outdoors' improved significantly (-34.1%; p= .001), whereas non-significant improvement trends were observed in the domains of 'family-role' (-21.8%; p= .055) and 'job and education' (–17.6%; p= .088). Improvements also occurred in the HRQoL domains of 'physical functioning' (11.5%; p= .007) and 'vitality' (21.5%; p= .019). There was a non-significant improvement trend (17.1%; p= .080) in the HRQoL domain of 'change in health,' which measured patients' health perceptions compared to one year prior to the study.

Discussion

To the best of our knowledge, this is the first report of the effects of a physical intervention on health-related daily functioning, participation, and HRQoL among long-term LTx recipients. This study shows that a 12-week supervised exercise training program plus activity counseling improves health-related daily functioning in fatigued LTx recipients. Furthermore, we observed a favourable effect on several participation and HRQoL domains.

The observed baseline health-related daily functioning score (10.4) was comparable to that reported by Holzner et al.[29] for long-term LTx recipients (9.9). The 23.6% improvement is significant, and shows that a rehabilitation program can be effective in improving health-related daily functioning after LTx. The improvements in participation

Table 1. Baseline characteristics for 18 liver transplant recipients

Number of patients	18
Sex	
Men	10
Women	8
Age in years	51.0 (33.9 - 62.5)
Time since transplantation in years	7.5 (1.3 - 17.0)
Primary liver disease (n) [a]	
Chronic	13
Acute	5
Number of immunosuppressive agents (n) [b]	
1	13
2	3
3	2
Home situation	
Married/co-habiting	11
Living alone	7
Children living at home	
Yes	7
No	11
Employment	
Strenuous activity	3
Light activity	4
No job	11
Participates in sports	
Yes	7
No	11
Anxiety score [c]	5.5 (0 - 14)
Depression score [c]	5.8 (1 – 13)

Results are presented as mean (range) or number of patients

[a] Chronic primary disease: viral (n=3), cholestatic (n=3), autoimmune cirrhosis (n=1), cryptogenic cirrhosis (n=4), Wilson's disease (n=1), polycystic liver disease (n=1); Acute primary disease: viral (n=1), acute liver failure e causa ignota (n=2), auto immune hepatitis (n=1), Wilson's disease (n=1)

[b] Immunosuppressive agents: 1 agent: tacrolimus (n=8), cyclosporine (n=3), mycophenolate (n=1) or everolimus (n=1); 2 agents: prednisone with tacrolimus (n=2), or prednisone with cyclosporine (n=1); 3 agents: prednisone with tacrolimus and azathioprine (n=1), prednisone with cyclosporine and mycophenolate (n=1)

[c] Data obtained by Hospital Anxiety and Depression Scale[18]

Table 2. Effects of a 12-week rehabilitation program on daily functioning, participation, and health-related quality of life (n=18)

	Pre-intervention score	Post-intervention score	Change	p-value
Health-related daily functioning (SIP-68)	10.39 (6.03)	7.94 (7.22)	-23.6%	.007*
Participation (IPA)				
Autonomy indoors	0.42 (0.47)	0.31 (0.44)	-26.2%	.208
Family role	1.56 (0.89)	1.22 (0.63)	-21.8%	.055†
Autonomy outdoors	1.82 (0.67)	1.20 (0.56)	-34.1%	.001*
Social relations	1.06 (0.54)	1.08 (0.73)	1.9%	.833
Job and education	2.33 (1.30)	1.92 (1.09)	-17.6%	.088†
Health-related Quality of Life (RAND-36)				
Physical functioning	67.5 (16.4)	75.3 (16.8)	11.5%	.007*
Social functioning	73.6 (19.6)	77.8 (15.8)	5.7%	.380
Role limitations physical	68.1 (31.9)	51.4 (44.9)	-24.5%	.178
Role limitations emotional	37.0 (42.6)	35.2 (43.5)	-5.0%	.904
Mental health	72.7 (18.0)	73.3 (19.5)	3.3%	.627
Vitality	7.8 (12.6)	58.1 (18.5)	21.5%	.019*
Bodily Pain	71.9 (25.7)	82.3 (26.9)	14.5%	.176
General health perception	50.6 (20.5)	54.2 (22.6)	7.1%	.336
Change in health	56.9 (22.4)	66.7 (21.0)	17.1%	.083†

Results are presented as mean (SD)
SIP: Sickness Impact Profile.[20] Higher scores indicate lower health-related daily functioning
IPA: Impact on Participation and Autonomy.[26] Higher scores indicate more restrictions in participation
RAND-36: validated Dutch version of the Short Form Health Survey-36.[27] Higher scores indicate higher levels of HRQoL
* Significant ($p \leq .05$) difference
† Difference at the $\alpha = .10$ level (trend)

scores were comparable to the gains in health-related daily functioning. However, the participation domains of 'autonomy indoors' and 'social relations' did not change, possibly indicating a ceiling effect in LTx recipients.

Our results are consistent with other studies that show the favourable effects of exercise training on HRQoL in other patient groups.[11-13] The improvements in the HRQoL domains 'physical functioning' and 'vitality' are consistent with previous findings that the physical HRQoL domains improve with exercise training in patients with chronic disease.[10] Surprisingly, the physical HRQoL domain 'role limitations physical' showed a non-significant decrease after the intervention. This may have

occurred because the mean baseline score (68.1) was already near the mean score for the Dutch healthy population (76.1).[28] We further speculate that, although patients had improved physical functioning after the program, these improvements did not meet patient expectations for desired physical activity at work and in other daily activities. Unlike Krasnoff et al.[15], we found no improvement in the 'general health' domain. It is possible that a 12-week rehabilitation program is too short to affect feelings about general health among patients transplanted at least one year previously.

The proportion of LTx recipients with HADS indicators for depression (22%) or anxiety (17%) was somewhat lower compared to our previous longitudinal study.[7] Selection bias may explain this finding; patients who participate in an intensive 12-week rehabilitation program may be less likely to have anxiety or depression at baseline.

The two major limitations of this study were the lack of a control group and a possible lack of generalizability to the general LTx population. We performed an uncontrolled intervention study, because this was the first study to assess such an intensive physical rehabilitation program (supervised training twice weekly) among fatigued LTx patients. Our previous study showed that, without intervention, health-related daily functioning, and HRQoL remains impaired in LTx recipients.[7] However, a randomized controlled trial is needed to draw stronger conclusions about the effect of rehabilitation on health-related daily functioning, participation, and HRQoL in fatigued LTx recipients. There is also a possible lack of generalizability because of the small study sample and selection bias at the time of patient recruitment. Participants are more likely to be highly motivated at baseline, as illustrated by their willingness to attend two exercise sessions per week for 12 weeks at our rehabilitation department. Furthermore, participants may not be representative of the general LTx population because they had no contraindications for exercise or maximal ergometer testing. Also, because we only recruited fatigued patients, it is difficult to generalize the results to the total LTx population. However, we believe that our results can be generalized to fatigued LTx recipients who do not have contraindications for exercise or maximal ergometer testing.

In conclusion, short-term rehabilitation using supervised exercise training and daily activity counseling can positively impact daily functioning, participation, and HRQoL among fatigued LTx recipients. Future research is needed to explore the mechanisms responsible for these improvements.

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Chapter 8

General Discussion

Fatigue after Liver Transplantation

Liver transplantation (LTx) is the treatment of choice for end-stage liver disease as it is associated with excellent mid-term and long-term outcomes.[1] Studies show that patients experience improved health-related quality of life (HRQoL) following LTx, but that HRQoL does not reach that of the healthy population.[2] Fatigue is one of the most common symptoms for liver transplant recipients.[3, 4]

In this thesis, we addressed several aims. First, we evaluated fatigue severity after LTx using a cross-sectional study of 96 LTx recipients (Chapter 2). Second, we aimed to determine associations between fatigue after LTx and personal and medical factors, HRQoL, health-related daily functioning, sleep quality, anxiety and depression using a longitudinal study of 70 LTx recipients (Chapter 3). We also performed cross-sectional studies of LTx recipients to determine the association between fatigue severity and physical fitness (18 patients) (Chapter 4), and fatigue severity and daily physical activity (PA) level (8 patients) (Chapter 5). Furthermore, we conducted an uncontrolled intervention study to determine the feasibility and effects of a rehabilitation program, consisting of a supervised exercise training program and PA counseling, on fatigue, physical fitness, daily PA level, health-related daily functioning, participation, and HRQoL in 18 fatigued LTx recipients (Chapters 6 and 7).

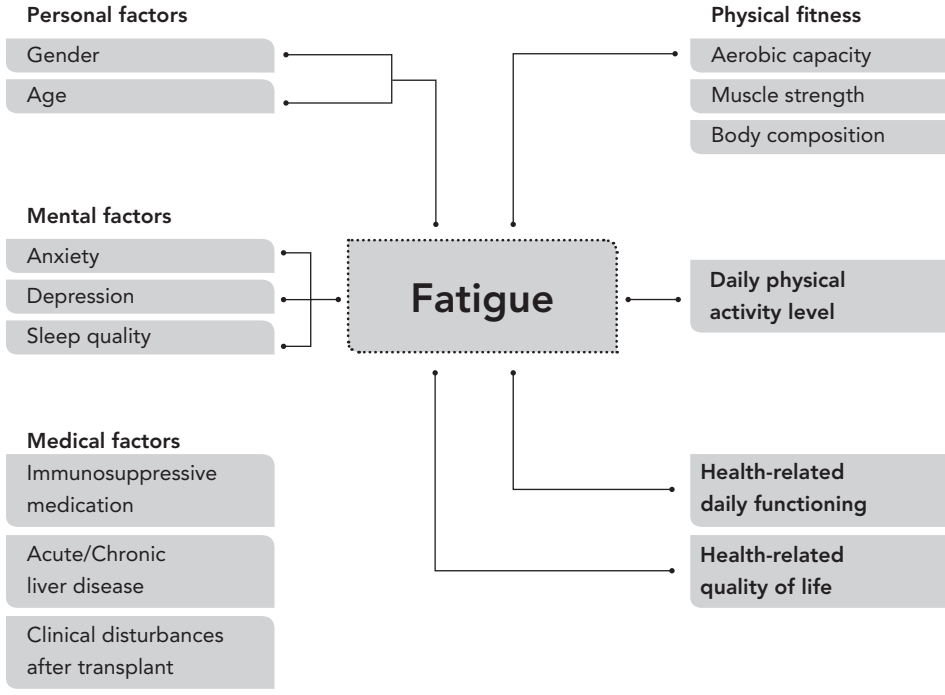
Main findings

Severity of fatigue and associated factors

Fatigue is a major problem after LTx, with 66% of studied LTx recipients reporting this symptom (Chapter 2). Although one would expect fatigue to decrease after LTx, fatigue severity is actually higher in LTx recipients compared to non-transplanted patients with primary biliary cirrhosis, a chronic liver disease. A follow-up assessment of LTx patients showed no improvement in fatigue levels over time, suggesting that fatigue after LTx is chronic (Chapter 3).

Figure 1 shows factors associated with fatigue in LTx recipients. In our study, women and older LTx recipients were more fatigued compared to men and younger patients. Fatigue severity was related to health-related daily functioning and HRQoL, suggesting that reducing fatigue may improve these two health domains. Depression, anxiety and sleep quality were also associated with fatigue. Compared to the general population, LTx recipients reported more depressed moods and sleep disturbances (Chapter 3).

Figure 1. Factors associated with fatigue in liver transplant recipients



LTx recipients' aerobic capacity was impaired and obesity was more prevalent compared to the general population. There were no indications that muscle strength was impaired after LTx. We found an association between fatigue and aerobic capacity (Chapter 4), suggesting that improving aerobic capacity may reduce fatigue after LTx. Despite the finding that LTx recipients in our study had normal activity levels, we found an association between fatigue and daily PA level, suggesting that improving level of daily PA may reduce fatigue after LTx (Chapter 5). We found no associations between

fatigue severity and the following medical factors: type of immunosuppressive agents and indication for transplantation (acute or chronic liver disease) (Chapter 2). In our longitudinal study (Chapter 3), we found no indications that major events (rejection, de novo cancer, infection, and disease recurrence) or changes in clinical factors (immunosuppressive agents, liver function, kidney function, hemoglobin, or body weight) in the period after LTx, were accompanied by changes in fatigue, suggesting that fatigue after LTx is not caused by medical factors.

Benefits of rehabilitation

We found that a 12-week rehabilitation program designed to increase physical fitness and daily PA level was feasible and effective in reducing fatigue, and improving aerobic capacity, increasing muscle strength and decreasing body fat in fatigued LTx recipients. The LTx recipients did not increase their daily PA levels after the program, indicating that there were no behavioural changes. Cardiovascular disease risk (lipid profiles and glycemic control) did not change after the program. Moreover, there were no long-term benefits on fatigue (Chapter 6). However, our rehabilitation program was effective in improving health-related daily functioning, most participation domains, and physical HRQoL domains (Chapter 7).

Methodological issues

Generalizability

We believe that results from the cross-sectional study of fatigue severity can be generalized to the general LTx population because of our consecutive sampling design (Chapter 2), which included nearly half of all LTx recipients treated in the Erasmus University Medical Center. However, there are some limitations to the generalizability of these findings. First, the reported fatigue severity of patients from the follow-up study (Chapter 3) may underestimate fatigue in the general LTx patient population, because non-participants were more fatigued at baseline compared to patients who participated in baseline and follow-up measurements. Secondly, the small sample sizes in the other studies presented in this thesis may limit the generalizability of our findings. Thirdly, in the studies assessing physical fitness training, fitness testing or both, about 25% of LTx recipients were excluded because of exercise or maximal

ergometer test contraindications (Chapters 4, 6 and 7). Because we only recruited fatigued patients without contraindications for exercise or maximal ergometer testing, it is difficult to generalize the intervention effects to the general LTx population (Chapters 6 and 7). Regardless of these limitations, we believe that our results can be generalized to fatigued LTx recipients who do not have contraindications for exercise or maximal ergometer testing.

Selection bias may have occurred for some studies because more active or fit patients may be more interested in participating in studies that include physical fitness training, fitness testing or daily PA measurements (Chapters 4, 5, 6 and 7).
This selection bias may lead to an overestimation of daily PA and physical fitness levels. However, because all participants had baseline fatigue, it is unlikely that only active and fit patients participated. Selection bias also may have occurred in the intervention study (Chapters 6 and 7); participants were likely highly motivated, as evidenced by their willingness to attend two weekly exercise sessions for 12 weeks at our rehabilitation department.

Factors associated with fatigue

Although we found associations between fatigue and gender, age, anxiety, depression, sleep quality, aerobic capacity, PA level, health-related daily functioning and HRQoL (Figure 1, Chapters 2, 3, 4 and 5), we cannot draw conclusions about the direction of these relationships. Moreover, small sample sizes may have limited our ability to detect statistically significant associations. The factors we found to be associated with fatigue may, therefore, be incomplete. Other factors, such as work, attitude, coping, sociocultural background, anaemia, cognitive dysfunction, and alternations in central neurotransmission were not studied, but may be associated with fatigue as well.[5-8]

Depression often relates to fatigue, but fatigue can occur without depression, as in Parkinson's disease, multiple sclerosis, and stroke.[9-11] In our follow-up study, we found that 39% of fatigued or severely fatigued patients also had depressive symptoms, indicating that the majority of fatigued patients had no symptoms of depression.

It is interesting to unravel the problem of fatigue after LTx. Because fatigue is a multidimensional concept, research on causes of fatigue should include large samples and more extensive tests than were performed in this thesis. In this thesis, we tried to determine starting points to develop fatigue-reducing intervention programs within a rehabilitation context.

Design of intervention study

We performed an uncontrolled intervention study, because this study was the first step to test the feasibility of an intensive physical rehabilitation program (supervised training twice weekly) among fatigued LTx recipients and to study possible effects on fatigue. The follow-up study showed that, in the absence of intervention, LTx recipients experience persistent fatigue, as well as impaired health-related daily functioning and HRQoL (Chapter 3). However, a randomized controlled trial is needed to confirm our findings about the effect of rehabilitation on fatigue.

Intervention

The rehabilitation program used in the intervention study consisted of exercise training and daily activity behaviour counseling sessions (Chapters 6 and 7). Exercise training was based on aerobic bicycle training and muscle strength training from the 'Recovery & Stability' program in cancer survivors, and showed benefits on aerobic capacity and muscle strength.[12] Although our cross-sectional study showed no baseline muscle strength deficits and no apparent association between muscle strength and fatigue (Chapter 4), we included muscle strength training because other studies have shown muscle strength deficits in LTx recipients.[13-15] The muscle strength training program was of moderate intensity with a high number of repetitions, and elicits improvements in muscular endurance rather than optimizing muscular strength. Moderate muscular strength training is recommended because it best mimics everyday activities.[16]

Exercise training consisted of supervised, one-hour training sessions twice weekly. The American College of Sports Medicine (ACSM) recommends a training frequency of three to five days per week for healthy adults who wish to achieve and maintain optimal fitness.[16] However, the ACSM also notes that these guidelines should be considered in the context of individual needs, goals, and baseline abilities. Because of severe baseline fatigue, conflicts with work hours, and long travel distances to the training site, we limited patient training sessions to two times per week. Extended weekly training may have resulted in greater physical fitness improvements.

Daily activity behaviour counseling sessions were based on the 'Active after Rehabilitation' program in people with physical disabilities.[17] Each participant completed four sessions with a physical therapist, who identified possibilities,

facilitators and barriers to daily PA, and provided individualized PA advice. These personalized counseling sessions provided an opportunity for the counselor and patient to propose solutions to increase daily PA (as opposed to a top-down instruction by the counselor).

We included daily activity behaviour counseling in the rehabilitation program, despite our findings that LTx recipients had on average no baseline deficits in daily PA levels (Chapter 5). We expected fatigued intervention study participants to have low daily PA levels because low daily PA levels are associated with fatigue (Chapter 4). Therefore, daily activity behaviour counseling would be of added value to this patient group. Contrary to our expectations, baseline daily PA levels of fatigued intervention study participants were comparable to those of age and sex-matched healthy subjects. This may explain why there was no change in daily PA levels after the 12-week rehabilitation program. Another explanation for the lack of change is that the frequent exercise training visits (twice weekly for 12 weeks) may have placed additional burdens on patients, which negatively impacted patient efforts to increase daily PA levels. We did not measure the daily PA levels at follow-up. It may be possible that patients did not change their behaviour immediately, but that behavioural changes would occur some time after finishing the program.

Outcome measures

Fatigue

We used several different fatigue questionnaires throughout this thesis. In all studies, the Fatigue Severity Scale (FSS) was used to measure fatigue severity.[18] Most FSS items are related to behavioural consequences of fatigue, rather than fatigue characteristics. By using the Multidimensional Fatigue Inventory (MFI), we distinguished between mental and physical fatigue to better understand the nature of fatigue in LTx recipients (Chapter 2).[19] However, because we anticipated that mental and physical fatigue aspects may overlap, we decided to measure perceived fatigue, regardless of whether this fatigue is mental or physical, using the FSS, the Checklist Individual Strength (CIS-20) subscale severity of subjective feeling of fatigue, and a visual analog scale (VAS) for fatigue (Chapters 6 and 7). These fatigue measures overlap considerably and each scale has advantages and disadvantages. Although several studies recommend the standardized and validated FSS and CIS-20, ceiling effects have been

reported with these tools.[20-22] The VAS-fatigue has shown slightly lower reliability, but higher sensitivity to changing fatigue levels compared to longer and more complex fatigue instruments.[23] We used the FSS as backbone of this thesis, because it has been used extensively in several patient groups, including liver disease patients.[24, 25]

Daily physical activity

We measured daily PA objectively on two randomly selected consecutive weekdays (48-hour period) using an accelerometry-based activity monitor (AM). Due to technical limitations (battery use) and practical reasons (participants cannot shower during measurements), we limited the study to a two-day measurement. There is evidence suggesting that 24-hour AM measurements are sufficient to measure a person's level of daily PA, but others recommend three to five days.[26, 27] The variance was small between the first and second day measurements for our patients. This supports the assumption that two randomly selected consecutive days is sufficient to adequately assess daily PA level.

Health-related quality of life and health-related daily functioning

The Sickness Impact Profile (SIP-68)[28] is often used as an HRQoL questionnaire; however, we used it to assess daily functioning. It seems inaccurate to classify the SIP-68 as an HRQoL questionnaire because the term 'quality' implies subjectivity. Although there are some similarities between the SIP-68 and the Dutch Short-Form 36 health survey (RAND-36)[29], the RAND-36 is much more related to self-perception. Our description of the SIP-68 changed throughout this thesis from 'self-experienced disabilities' to 'health-related daily functioning.' The description 'self-experienced disabilities' does not seem suitable for the SIP-68. Although the SIP-68 is a self-assessment questionnaire, most SIP-68 statements are concrete and observable, leaving little leeway for subjectivity in assessing self-perception.

Clinical implications

This is the first study of fatigue after LTx. The results of this thesis indicate that fatigue is a chronic problem after LTx, which impacts patients' health-related daily functioning and HRQoL (Chapters 2 and 3). With increasing survival rates for LTx recipients,

and a shift in focus towards improved HRQoL, the problem of fatigue should be acknowledged in health care. The etiology of fatigue after LTx is unknown. However, we found that in addition to age and gender, anxiety, depression, sleep quality, aerobic capacity and PA level were also associated with fatigue (Chapters 2, 3, 4 and 5). These latter associations may provide starting points for successful fatigue-reducing interventions. We showed that physical rehabilitation, consisting of exercise training and daily activity behaviour counseling, may be useful in managing fatigue after LTx (Chapter 6).

In other patient groups (cancer and chronic fatigue syndrome patients), research on various fatigue-reducing interventions has increased considerably over the last few years.[30-34] Examples of fatigue-reducing interventions that have been studied include cognitive behavioural therapy (CBT), exercise, prolonged rest, antidepressants and homeopathy. Another reason to study physical rehabilitation in LTx recipients is for the possible benefits to physical fitness (aerobic capacity, muscle strength and body fat). Physical fitness, an important component of health, appears to be associated with improved functioning and well-being in patients with a chronic disease.[35, 36] Our rehabilitation program participants also showed improvements in health-related daily functioning, most participation domains, and physical HRQoL domains (Chapters 6 and 7). The research reported in this thesis provides a starting point for future studies to determine the mechanisms of fatigue after LTx and to develop fatigue-reducing interventions that have long-term effects. Future research with larger study samples is needed to determine the mechanism of the improvements reported here and to optimize interventions for LTx recipients.

Recommendations for future research

Factors associated with fatigue

In this thesis we studied several factors that are associated with fatigue after LTx, and identified starting points for a physical rehabilitation program. Chronic fatigue often has multiple or unknown causes. Although this is the first study of its kind among LTx recipients, studies in other fatigued populations have examined factors such as work, attitude, coping, sociocultural background, anaemia, cognitive dysfunction, and alternations in the central neurotransmission.[5-8] We found no indications that fatigue was related to immunosuppressive medications, liver disease etiology, clinical

disturbances, or comorbidities. This lack of associations suggests that fatigue after LTx is not caused by medical factors. However, more research with larger study samples and more extensive testing should be performed to determine causes of fatigue after LTx.

Moreover, although depression has been associated with fatigue in patients with cancer and chronic fatigue syndrome, the association does not imply causation.[6, 37, 38] Fatigue and depression may both result from another underlying factor. Or, if causality does exist, fatigue could be a symptom of depression or fatigue may lead to depressive feelings. In our study, 39% of patients with fatigue or severe fatigue also endorsed depressive symptoms. Because most patients were not depressed, fatigue after LTx cannot be explained by depression alone. Future studies using different depression instruments should be performed to evaluate the association between fatigue and depression after LTx.

Interventions

We showed that physical rehabilitation, consisting of exercise training and daily activity behaviour counseling, is associated with fatigue reduction after LTx. However, randomized controlled trials (RCTs) with larger samples are needed to draw stronger conclusions about these effects. Our patient database included 228 patients aged 18 to 65 years who had undergone LTx more than one year prior to study initiation. Only twenty patients were included in the intervention study. Patients were excluded for: 1) contraindications for exercise or maximal ergometer test, 2) lack of interest, and 3) lack of fatigue at baseline. RCTs require large study samples to ensure sufficient power to detect treatment effects. To achieve these large sample sizes, collaboration with other LTx centers is needed. Moreover, future intervention studies should better accommodate patients with convenient study locations to minimize conflict with work and non-participation because of fatigue associated with getting to the study site. These changes will also allow for the recommended three training sessions per week.[16]

On average, patients in our intervention study were 7.5 years post-transplantation. It is possible that an intervention conducted closer to the time of LTx may be associated with greater impact on fatigue. Patients are closely medically followed in the first year post-transplantation, which provides an ideal opportunity to encourage healthy behaviours such as regular exercise and PA. However, to account for improvements due to natural recovery in the first year after LTx, a control group receiving standard

supportive care would be necessary. Future studies should also focus on developing and testing fatigue-reducing interventions with sustained long-term effects on fatigue, physical fitness and daily activity behaviour.

The intervention study described in this thesis was the first attempt to manage fatigue after LTx. Exercise-based interventions often have beneficial effects on fatigue.[39-42] However, a variety of interventions have been studied to reduce fatigue in different patient groups.[30-34, 43] Because we also found that fatigue was associated with anxiety, depression and sleep quality, interventions to address these issues may also improve fatigue after LTx. It would be instructive to study whether other fatigue-reducing interventions are also beneficial in LTx recipients.

Cognitive Behavioural Therapy

CBT is a general form of psychotherapy directed at changing condition-related cognitions and behaviours. In cancer survivors and patients with chronic fatigue syndrome, CBT has shown success in reducing chronic fatigue.[30, 34] A long-term follow-up study of cancer survivors show that the positive effects of CBT are maintained years after treatment.[44] CBT is directed at cognitions and behaviours relevant to a specific disorder, so CBT for fatigue after LTx would not be the same as CBT for cancer survivors or CBT for chronic fatigue syndrome patients. It is worthwhile to study the effects of a CBT program designed for LTx recipients in future RCTs. However, to develop such a CBT program, more information is needed about the factors responsible for perpetuating fatigue in LTx recipients.

Improving physical fitness and physical activity

Therapeutic exercise training is not routinely included in medical care after LTx. In addition to reducing fatigue, LTx recipients would benefit from improved daily PA and physical fitness. Although LTx recipients showed no baseline deficits in daily PA compared to the general population, the average healthy person has a physically inactive lifestyle and could benefit from increases in daily PA. Patients with inactive lifestyles have higher risks of morbidity, mortality and several chronic diseases, including cardiovascular disease, diabetes, osteoporosis, and several forms of cancer.[45] Improving daily PA and physical fitness levels for LTx recipients is likely more important than it is in the general population. Although obesity and overweight are

highly prevalent among LTx recipients, our intervention did not include a weight reduction program. In addition to exercise training and stimulating daily PA, future physical rehabilitation programs should also focus on dietary behaviour and weight management.

In conclusion, this thesis showed that fatigue is a major problem after LTx that deserves attention from health care providers and researchers. We showed that physical rehabilitation is effective in reducing this fatigue. Randomized controlled trials should confirm these results and address long-term effects.

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Sum

The introductory **Chapter 1** describes the shift in focus from the management of rejections, short-term complications, and patient survival after liver transplantation (LTx) to the prevention of long-term complications and health-related quality of life (HRQoL) improvement. Although HRQoL improves markedly after LTx, patients still show considerable deficits compared to the healthy population. Outcomes of HRQoL studies and the observation of medical specialists that LTx recipients often experience fatigue, gave rise to the research project described in this thesis. In this thesis, we defined fatigue as "a perception of a lack of energy, or a feeling of tiredness that affects mental and physical activity, which differs from sleepiness or lack of motivation. Fatigue may be aggravated by, but is not primarily attributed to, exertion or diagnosable disease". Studies about prevalence of fatigue after LTx are lacking. Moreover, knowledge of the factors associated with fatigue after LTx is necessary for the development of fatigue-reducing interventions in the LTx population. Therefore, this thesis aims to explore the severity of fatigue among LTx recipients and its associations with personal and medical factors, sleep quality, anxiety, depression, physical fitness, level of daily physical activity (PA), daily functioning, and HRQoL. Furthermore, we studied the feasibility and effect of a rehabilitation program, which aimed at improving physical fitness and daily PA, on fatigue, physical fitness, daily PA, daily functioning, participation, and HRQoL in fatigued LTx recipients.

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Chapter 2 shows that fatigue is a major problem after LTx; 66% percent of the 96 studied LTx recipients was fatigued or severely fatigued as measured with the Fatigue Severity Scale (FSS). Women and older LTx recipients were more fatigued than men and younger LTx recipients. Severity of fatigue was associated with health-related daily functioning and HRQoL, suggesting that it is likely that by reducing fatigue, health-related daily functioning and HRQoL can be improved. We found no association between time since transplantation and severity of fatigue, indicating that complaints do not change over time. Moreover, severity of fatigue was not associated with indication for liver transplantation or number of immunosuppressive agents.

In **Chapter 3** we studied 70 LTx recipients who had participated in the study described in Chapter 2 and reassessed them at two years to gain insight in the time course of fatigue following LTx. Results show that fatigue is a chronic problem after LTx and that health-related daily functioning and HRQoL remained stable over time. Individual changes in fatigue were associated with changes over time in daily functioning and most HRQoL domains. Compared to the general population, LTx recipients reported being more depressed and the prevalence of sleep disturbances was higher. Sleep quality, anxiety, and depression were also associated with fatigue severity. Individual changes in fatigue were not associated with major events (rejection, de novo cancer,

infection, recurrence of disease) or changes in clinical factors (immunosuppressive agents, liver function, kidney function, hemoglobin, body weight) during the studied two years.

Chapter 4 studies physical fitness (aerobic capacity, muscle strength, body composition) in LTx recipients. Results showed that LTx recipients had an impaired aerobic capacity and that the prevalence of obesity was higher than in the general population. We found no deficits in muscle strength. Aerobic capacity was related to severity of fatigue, suggesting that improving aerobic capacity might reduce fatigue by breaking the negative cycle of fatigue, inactivity, and deconditioning in LTx recipients. In addition, we found associations between physical fitness (particularly aerobic capacity) and several aspects of HRQoL, suggesting that improving physical fitness may result in improved HRQoL in LTx recipients.

Chapter 5 studies level of daily PA in LTx recipients using an accelerometry-based activity monitor. Results showed that LTx recipients were not significantly less active than comparison subjects. Level of daily PA was related to severity of fatigue, suggesting that improving the level of daily PA might reduce fatigue by breaking the negative cycle of fatigue, inactivity, and deconditioning in LTx recipients. In addition, we found associations between level of daily PA and several aspects of HRQoL, suggesting that a more active lifestyle might improve HRQoL in LTx recipients.

In **Chapter 6** we evaluated the feasibility and effects of a 12-week rehabilitation program designed to improve physical fitness and daily PA, on fatigue, physical fitness, and daily PA in fatigued LTx recipients. We found that rehabilitation using supervised exercise training and daily physical activity counseling is feasible and effective in reducing fatigue and improving physical fitness in fatigued LTx recipients. Daily PA and cardiovascular disease risk (lipid profiles and glycemic control) did not change after the program. Moreover, the program demonstrated no long-term benefits on fatigue. We suggested that a randomized controlled trial is needed to draw stronger conclusions about the effect of rehabilitation on fatigue and that future research with larger study samples is needed to determine the mechanism of this decreased fatigue and to develop long-term fatigue-reducing interventions for LTx recipients.

In **Chapter 7** we aimed to study whether the fatigue-reducing 12-week exercise training program plus daily activity counseling as described in Chapter 6, is also beneficial in improving health-related daily functioning, participation, and HRQoL in fatigued LTx recipients. After the program, LTx recipients showed improvements in health-related daily functioning, most participation domains and physical HRQoL domains. We suggested that a randomized controlled trial is needed to draw stronger conclusions about the effect of rehabilitation on health-related daily functioning, participation, and HRQoL and that future research with larger study samples is needed to determine the mechanism of these improvements.

Finally, **Chapter 8** addresses the main findings of the studies and discusses some methodological issues, including the generalizability of the results, choice of starting points for developing fatigue-reducing intervention programs, the strengths and limitations of the intervention program, and choice of outcome measures.
We presented the clinical implications of our findings, concerning the importance of fatigue-reducing interventions among LTx recipients and benefits of physical rehabilitation programs as fatigue-reducing interventions after LTx. Finally, we provided suggestions for future research.

Samen

Het inleidende **hoofdstuk 1** toont dat er op het gebied van levertransplantatieonderzoek de laatste decennia een verschuiving heeft plaatsgevonden. Voorheen richtte het onderzoek zich vooral op de behandeling van afstoting, het voorkomen van complicaties op korte termijn, en de overleving van de patiënt. Tegenwoordig wordt er steeds meer onderzoek gedaan naar het voorkomen van complicaties op langere termijn en het verbeteren van de kwaliteit van leven bij mensen die een levertransplantatie (LTx) hebben ondergaan. Ondanks een verbetering in de kwaliteit van leven na transplantatie in vergelijking met de periode voor transplantatie, blijft deze aanmerkelijk lager dan bij personen zonder aandoening. Uit de resultaten van diverse onderzoeken naar kwaliteit van leven blijkt dat vermoeidheid één van de grootste problemen is na LTx. Dit gegeven gaf, samen met de observatie van medisch specialisten in het Erasmus Universitair Medisch Centrum dat LTx patiënten vaak met vermoeidheid kampen, aanleiding tot de onderzoeken die beschreven zijn in dit proefschrift.

In dit proefschrift definieerden we vermoeidheid als "een waarneming van gebrek aan energie of een gevoel van uitputting dat invloed heeft op mentale en fysieke activiteit en afwijkt van slaperigheid en gebrek aan motivatie. Vermoeidheid kan worden verergerd door, maar is niet primair het gevolg van inspanning of een diagnosticeerbare ziekte." Er is een gebrek aan onderzoeken naar de prevalentie van vermoeidheid na LTx. Bovendien is voor de ontwikkeling van interventies die vermoeidheid na LTx kunnen verminderen, inzicht nodig in de factoren die met deze vermoeidheid samenhangen. Het doel van dit proefschrift is daarom inzicht te krijgen in de ernst van vermoeidheid in de LTx populatie en haar relaties met persoonlijke en medische factoren, slaapkwaliteit, angst, depressie, fysieke fitheid, dagelijkse lichamelijke activiteit, dagelijks functioneren en kwaliteit van leven. Tevens bestudeerden we de toepasbaarheid en effectiviteit van een revalidatieprogramma

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gericht op het verbeteren van fysieke fitheid en dagelijkse lichamelijke activiteit, op vermoeidheid, fysieke fitheid, dagelijkse lichamelijke activiteit, gezondheidsgerelateerd dagelijks functioneren, participatie en gezondheidsgerelateerde kwaliteit van leven.

Hoofdstuk 2 laat zien dat vermoeidheid een groot probleem na LTx was: 66% van de bestudeerde LTx patiënten was vermoeid of ernstig vermoeid zoals gemeten met de Fatigue Severity Scale, een vermoeidheidsvragenlijst. Vrouwelijke en oudere LTx patiënten waren vermoeider dan respectievelijk mannelijke en jongere LTx patiënten. De ernst van vermoeidheid hing samen met gezondheidsgerelateerde dagelijks functioneren en gezondheidsgerelateerde kwaliteit van leven. Het lijkt dus aannemelijk dat door het verminderen van vermoeidheid, het gezondheidsgerelateerde dagelijks functioneren en de gezondheidsgerelateerde kwaliteit van leven zouden kunnen worden verbeterd. We vonden geen relatie tussen tijd na transplantatie en ernst van vermoeidheid, wat suggereert dat de klachten na verloop van tijd niet verminderen. Tevens was de ernst van vermoeidheid niet gerelateerd aan indicatie voor levertransplantatie of aantal immunosuppressiva.

In het onderzoek dat is beschreven in **Hoofdstuk 3** bestudeerden we 70 LTx patiënten die ook deelnamen aan het onderzoek dat beschreven is in hoofdstuk 2 en onderzochten hen na twee jaar opnieuw om inzicht te krijgen in het verloop van de vermoeidheid na LTx. De resultaten toonden aan dat vermoeidheid een chronisch probleem is na LTx en dat gezondheidsgerelateerde dagelijks functioneren en gezondheidsgerelateerde kwaliteit van leven ook onveranderd bleven in de periode na LTx. Individuele veranderingen in vermoeidheid hingen samen met veranderingen in gezondheidsgerelateerde dagelijks functioneren en het merendeel van de gezondheidsgerelateerde kwaliteit van leven domeinen. In vergelijking met

een Nederlandse referentie populatie gaven de LTx patiënten aan meer depressieve klachten en slaapproblemen te hebben. Slaapkwaliteit, angst en depressie waren ook gerelateerd aan vermoeidheid. Individuele veranderingen in vermoeidheid waren niet gerelateerd aan ingrijpende gebeurtenissen (afstoting, kanker, infectie, terugkeer van ziekte) of veranderingen in klinische factoren (immunosuppressiva, leverfunctie, nierfunctie, hemoglobine, lichaamsgewicht) gedurende de periode van twee jaar.

Het onderzoek zoals beschreven in **Hoofdstuk 4** bestudeert de fysieke fitheid (aërobe capaciteit, spierkracht, lichaamssamenstelling) van LTx patiënten. De resultaten toonden aan dat LTx patiënten een verminderde aërobe capaciteit hadden en dat de prevalentie van obesitas hoger was dan in een Nederlandse referentie populatie. We vonden geen beperkingen in spierkracht. Aërobe capaciteit was gerelateerd aan ernst van vermoeidheid, hetgeen suggereert dat het verbeteren van de aërobe capaciteit zou kunnen leiden tot een vermindering in vermoeidheid door middel van het doorbreken van de negatieve vicieuze cirkel van vermoeidheid, inactiviteit en deconditionering na LTx. Bovendien vonden we relaties tussen fysieke fitheid (vooral aërobe capaciteit) en verschillende gezondheidsgerelateerde kwaliteit van leven domeinen, hetgeen suggereert dat het verbeteren van fysieke fitheid zou kunnen leiden tot een verbetering van gezondheidsgerelateerde kwaliteit van leven na LTx.

Hoofdstuk 5 beschrijft de dagelijkse lichamelijke activiteit van LTx patiënten gemeten met een activiteitenmonitor die gebruik maakt van versnellingssensoren. De resultaten toonden aan dat LTx patiënten niet minder actief waren dan vergelijkingspersonen. Dagelijkse lichamelijke activiteit was gerelateerd aan ernst van vermoeidheid, hetgeen suggereert dat het verhogen van de dagelijkse lichamelijke activiteit zou kunnen leiden tot een vermindering in vermoeidheid door middel van het doorbreken van de negatieve vicieuze cirkel van vermoeidheid, inactiviteit en deconditionering na LTx.

In het onderzoek zoals beschreven in **Hoofdstuk 6** evalueerden we de toepasbaarheid en effectiviteit van een 12 weken durend revalidatieprogramma op vermoeidheid, fysieke fitheid en dagelijkse lichamelijke activiteit bij vermoeide LTx patiënten. We vonden dat revalidatie, bestaande uit gesuperviseerde fitheidstraining en counseling ter verhoging van dagelijkse lichamelijke activiteit, toepasbaar was en effectief was in het verminderen van vermoeidheid en het verbeteren van fysieke fitheid bij vermoeide LTx patiënten. Dagelijkse lichamelijke activiteit en het risico op hart- en

vaatziekten (lipidenprofiel en glycemische controle) bleven onveranderd na het programma. Ook resulteerde het programma niet in een langdurige afname van vermoeidheidsklachten. We gaven aan dat een gerandomiseerd gecontroleerd onderzoek nodig is om sterkere conclusies te kunnen trekken over het effect van revalidatie op vermoeidheid. Toekomstig onderzoek met grotere patiëntenaantallen is nodig om het werkingsmechanisme van de interventie vast te stellen en om vermoeidheidsreducerende interventies met lange termijn effecten te ontwikkelen voor LTx patiënten.

In het onderzoek beschreven in **Hoofdstuk 7** onderzochten we of het vermoeidheidsreducerende 12 weken durende revalidatieprogramma - zoals beschreven in Hoofdstuk 6 - ook gunstige effecten had op het verbeteren van gezondheidsgerelateerde dagelijks functioneren, participatie en gezondheidsgerelateerde kwaliteit van leven bij vermoeide LTx patiënten. Na het programma lieten de LTx patiënten een verbetering zien in het gezondheidsgerelateerde dagelijks functioneren, in het merendeel van de participatie domeinen en in de fysieke gezondheidsgerelateerde kwaliteit van leven domeinen. We gaven aan dat een gerandomiseerd gecontroleerd onderzoek nodig is om sterkere conclusies te kunnen trekken over het effect van revalidatie op het gezondheidsgerelateerde dagelijks functioneren, op participatie en op gezondheidsgerelateerde kwaliteit van leven en dat toekomstig onderzoek met grotere patiëntenaantallen nodig is om het werkingsmechanisme van de interventie vast te stellen.

Tot slot worden in **Hoofdstuk 8** de belangrijkste bevindingen van de onderzoeken besproken en worden enkele methodologische aspecten, zoals de generaliseerbaarheid van de resultaten, de keuze van de beginpunten voor de ontwikkeling van vermoeidheidsreducerende interventies, de krachten en beperkingen van de interventie en de keuze van uitkomstmaten bediscussieerd. We presenteren de klinische implicaties van onze bevindingen: het belang van vermoeidheidsreducerende interventies voor LTx patiënten en van fysieke revalidatieprogramma's als vermoeidheidsreducerende interventies na LTx. In het laatste deel van dit hoofdstuk geven we ook enkele suggesties voor toekomstig onderzoek.

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Prof. dr. Metselaar, Herold, ik heb je kritische blik op de artikelen, je directheid en je bereidheid me te helpen altijd zeer gewaardeerd. Hartelijk dank daarvoor.

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Of het nu ging om maximale inspanningstesten, het dragen van een meetkastje en

woord

beplakt zijn met tape zonder te kunnen douchen, bloedprikken, (veel!) vragenlijsten invullen of 24 keer naar Rotterdam komen om te trainen, niets was te gek voor jullie. Bedankt! Het ga jullie goed!

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Curricul

um vitae

Berbke van Ginneken was born in Nijmegen on the 30th of August 1982. After finishing her Atheneum at Dominicus College in Nijmegen in 2000, she started studying Human Movement Sciences at the Vrije Universiteit in Amsterdam. She did a research internship at the Sint Maartenskliniek (Institute of Research, Development and Education) in Nijmegen, studying the effects of a four-week training with a new hybrid FES-cycle in persons with spinal cord injury. In the last half year of her Masters, she conducted a second research internship at the Department of Rehabilitation Medicine, Erasmus University Medical Center in Rotterdam, studying the level of everyday physical activity and fatigue in liver transplant recipients. She finished the Master of Science education in 2004 with a major in rehabilitation medicine. After her graduation, she continued the study on fatigue after liver transplantation in Rotterdam as a junior researcher resulting in this PhD thesis. During her PhD, she also worked on the 'guerilla'-project on hand function in patients with Charcot-Marie-Tooth disease. She is currently working as a researcher and policy advisor at Rijndam Rehabilitation Center in Rotterdam.

PhD Portfolio

Summary of PhD training and teaching activities

Name PhD student: Berbke van Ginneken	PhD period: 2004-2009
Erasmus MC Department: Rehabilitation Medicine	Promotor: Prof. H.J. Stam
	Supervisors:
	Dr. H.J.G. van den Berg-Emons
Research School: None	Dr. G. Kazemier

1. PhD training	Year	Workload (Hours/ECTS)
General academic skills		
Onderzoeksmethoden voor het bewegings-apparaat. Research Institute MUSC, Rotterdam	2004	24 hours
Introduction for beginning PhD candidates	2006	4 hours
Biomedical English Writing and Communication	2007	3 ECTS
Research skills		
Statistical Course Lineaire regressie en variantie-analyse, Amsterdam	2007	30 hours
In-depth courses (e.g. Research school, Medical Training)		
Presentations		
- Presentation 'Pilot-onderzoek naar de dagelijkse activiteit en vermoeidheid van patiënten na een levertransplantatie' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2004	20 hours
- Presentation 'Niveau van dagelijks functioneren en vermoeidheidsklachten in patiënten bij een orthotope levertransplantatie' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2004	20 hours
- Presentation 'Niveau van dagelijks functioneren en vermoeidheidsklachten in patiënten bij een orthotope levertransplantatie', dept. of Gastroenterology and Hepatology, Rotterdam	2004	8 hours

- Presentation 'Vermoeidheid en fysieke fitheid na een levertransplantatie. Een explorerend onderzoek' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2005	20 hours
- Presentation 'Fysieke fitheid en vermoeidheid na een levertransplantatie', dept. of Gastroenterology and Hepatology, Rotterdam	2005	8 hours
- Presentation 'Physical fitness and fatigue after liver transplantation' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2006	20 hours
- Presentation 'Rehabilitation after liver transplantation? A study into the applicability and feasibility of rehabilitation in liver transplant recipients' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2006	20 hours
- Presentation 'Vermoeidheid na levertransplantatie' at the Halfjaarlijkse vergadering Vlaams-Nederlands Onderzoekgroep Chronische Vermoeidheid (VNO-Chrover), Nijmegen	2006	20 hours
- Presentation 'Physical fitness, fatigue and quality of life after liver transplantation' at the 42nd Congress of the European Society for Surgical Research (ESSR), Rotterdam	2007	20 hours
- Poster presentation 'Effect of rehabilitation on fatigue, daily activity and fitness in liver transplant recipients' at the VRA najaarscolloquium, Utrecht	2008	8 hours
- Poster presentation 'Effect of rehabilitation on daily physical activity, physical fitness and fatigue in liver transplant recipients' at the International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM), Rotterdam	2008	8 hours

- Presentation 'Effect of rehabilitation on fatigue in liver transplant recipients' at the research meeting, dept. of Rehabilitation Medicine, Rotterdam	2008	8 hours
- Presentation 'Effect of rehabilitation on fatigue in liver transplant recipients' at the 16th European Congress of Physical and Rehabilitation Medicine 'From cell to society', Brugge, Belgium	2008	8 hours
International conferences		
- The 42nd Congress of the European Society for Surgical Research (ESSR), Rotterdam	2007	24 hours
- International Conference on Ambulatory Monitoring of Physical Activity and Movement (ICAMPAM), Rotterdam	2008	24 hours
- The 16th European Congress of Physical and Rehabilitation Medicine 'From cell to society', Brugge, Belgium	2008	32 hours
Seminars and workshops		
- MUSC retraite 'Samenwerken in beweging III', Rotterdam	2004	8 hours
- MUSC retraite 'Samenwerken in beweging IV', Rotterdam	2006	8 hours
- Symposium '(Hand)cycling Revalidatie en Sport van Werkgroep VRA bewegen en sport', Zuidlaren	2007	8 hours
- Congres 'Sport en Beweegprogramma's. Effectiviteit in de klinische praktijk', Rotterdam	2008	8 hours
- VRA najaarscolloquium, Utrecht	2008	8 hours
- Symposium 'Conditie of Cognitie? De rol van lichamelijke activiteiten in de behandeling van het chronisch vermoeidheidssyndroom en vermoeidheid na kanker', Nijmegen	2008	8 hours

Didactic skills		
Other		
- Research meetings, dept. of Rehabilitation Medicine, Rotterdam	2004-2009	146 hours
2. Teaching activities	**Year**	**Workload (Hours/ECTS)**
Lecturing		
Supervising practicals and excursions		
Supervising Master's theses		
- Supervising of medical student (thesis)	2007/2008	50 hours
Other		
- Supervising of medical student (internship)	2005	30 hours

List of publications

van Ginneken BTJ, van den Berg-Emons HJG, Metselaar HJ, Tilanus HW, Stam HJ, Kazemier G. Physical rehabilitation after liver transplantation improves fatigue and fitness. **Submitted**

van Ginneken BTJ, van den Berg-Emons HJG, Metselaar HJ, Tilanus HW, Kazemier G, Stam HJ. Benefits of a rehabilitation program on daily functioning, participation and quality of life in liver transplant recipients. **Submitted**

van Ginneken BTJ, van den Berg-Emons HJG, van der Windt A, Tilanus HW, Metselaar HJ, Stam HJ, Kazemier G. Persistent fatigue in liver transplant recipients: a two-year follow-up study. **Provisionally accepted in Clinical Transplantation**

van Pomeren M, Selles RW, van Ginneken BTJ, Schreuders TA, Janssen WG, Stam HJ. The hypothesis of overwork weakness in Charcot-Marie-Tooth: a critical evaluation. **Journal of Rehabilitation Medicine, 2009; 41: 32-4**

Schreuders TA, Selles RW, van Ginneken BTJ, Janssen WG, Stam HJ. Sensory evaluation of the hands in patients with Charcot-Marie-Tooth disease using Semmes-Weinstein monofilaments. **Journal of Hand Therapy, 2008; 21: 28-34**

van Ginneken BTJ, van den Berg-Emons HJG, Kazemier G, Metselaar HJ, Tilanus HW, Stam HJ. Physical fitness, fatigue and quality of life after liver transplantation. **European Journal of Applied Physiology, 2007; 100: 345-353**

Selles RW, van Ginneken BTJ, Schreuders TA, Janssen WG, Stam HJ. Dynamometry of intrinsic hand muscles in patients with Charcot-Marie-Tooth disease. **Neurology, 2006; 12: 2022-2027**

van den Berg-Emons HJG, Kazemier G, van Ginneken BTJ, Nieuwenhuijsen C, Tilanus HW, Stam HJ. Fatigue, level of everyday physical activity and quality of life after liver transplantation. **Journal of Rehabilitation Medicine, 2006; 38: 124-129**

van den Berg-Emons HJG, van Ginneken BTJ, Wijffels M, Tilanus HW, Metselaar HJ, Stam HJ, Kazemier G. Fatigue is a major problem after liver transplantation. **Liver Transplantation, 2006; 12: 928-933**