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FATIGUE, LEVEL OF EVERYDAY PHYSICAL ACTIVITY AND QUALITY OF LIFE AFTER LIVER TRANSPLANTATION

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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.**
Design: **Case comparison.**
Subjects: **Eight persons 6–36 months after liver transplantation with varying severity of fatigue and 8 persons without known impairments (matched for gender, age, social situation and employment).**
Methods: **Activity levels were assessed during 2 randomly selected consecutive weekdays with an accelerometry-based Activity Monitor. In the transplantation group, severity of fatigue (Fatigue Severity Scale) and health-related quality of life (RAND-36) were also 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 ($p = 0.01$) with both duration of dynamic activities and intensity of everyday activity ($r_s = -0.81$ and -0.84, respectively). Activity level was correlated ($p \leq 0.05$) with several domains of health-related quality of life ($r_s = 0.72$–0.78).**
Conclusion: **As a group, liver transplant recipients were not significantly less active than comparison subjects. Activity level was related with severity of fatigue and health-related quality of life. These findings have implications for the development of interventions needed to rehabilitate persons after liver transplantation.**

Key words: fatigue, activities of daily living, quality of life, liver transplantation, rehabilitation.

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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 to liver transplantation, fatigue remained the most distressing symptom one year after the transplantation. In a previous study by our group (unpublished observation; principal author), 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. In most cases, the cause of 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. (6) (see below) were recruited from the outpatient clinic of the Erasmus 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: multi-organ transplant recipients, co-morbidity that might interfere with everyday physical activity, hypersensitivity to 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.

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Instruments

Level of everyday physical activity. For assessment of the level of everyday physical activity an AM (size: $15 \times 9 \times 3.5$ 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 4 accelerometers, a portable data recorder and a computer with analysis software (7). 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 1-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 (8–10). 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 (7). Furthermore, the AM can detect differences in the level of physical activity during everyday life between groups (11–13), which supports its validity and applicability in clinical research.

Four ADXL202 uniaxial piezo-resistive accelerometers were used (Analog Devices, Breda, The Netherlands, adapted by Temec Instruments, Kerkrade, The Netherlands; size: $1.5 \times 1.5 \times 1$ cm). One accelerometer was attached to each thigh (while standing, sensitive in the anteroposterior direction), and 2 were attached to the skin over the sternum (while standing, 1 accelerometer is sensitive in the anteroposterior direction and 1 in the 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 (14) (supplied by Temec Instruments BV, Kerkrade, The Netherlands). A detailed description of the activity detection procedure has been described previously (7, 11). 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 for a period of 48 hours. Data 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 (6). The FSS is a 9-item self-administered questionnaire. The mean score of the 9 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 (6, 15).

Health-related quality of life. HRQoL was assessed with a validated Dutch version (16) of the Medical Outcomes Study Short Form-36 (SF-36) (17), the RAND-36. 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 (18). Additionally, one single item assesses change in perceived health during the previous 12 months. All raw scale scores are linearly converted to a 0–100 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 2 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 3 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 the 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 2 times the SD. Comparisons between data were made using the Wilcoxon test for paired observations, and the Mann-Whitney U test or the χ^2 test for unpaired observations. Using the Spearman correlation coefficient (r_s) relationships between parameters were studied. A probability value $p \leq 0.05$ determined statistical significance. However, because of the small study population, also results on the $p = 0.10$ level are presented (trend).

RESULTS

General characteristics of the study population are given in Table I. In both groups, 4 men and 4 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 ($p = 0.04$) as a consequence of the liver disease or transplantation. Furthermore, all employed comparison subjects had physically passive jobs, whereas 2 of the employed liver transplant recipients had physically active jobs ($p = 0.07$). Three liver transplant recipients were unemployed, 2 of them as a consequence of the liver disease.

Table I. *General characteristics of the liver transplant recipients and comparison subjects (given as mean (SD) or numbers)*

	Liver recipients ($n = 8$)	Comparison subjects ($n = 8$)
Age (years)	46 (11)	48 (11)
Body mass (kg)	82.3 (13.7)	79.4 (13.2)
Height (m)	1.76 (0.10)	1.72 (0.05)
Body mass index (kg/m^2)	26.7 (4.1)	26.6 (4.4)
Employment situation		
employed/unemployed	5/3	7/1
full-time/part-time	0/5	4/3*
Type of work (Active/passive)†	2/3	0/7#
Social situation (Living alone/living with a partner)	0/8	1/7

*$p < 0.05$; #$p < 0.10$ (trend).
†Active/passive: denote physically active ("blue-collar") and physically non-active ("white-collar") work.

Table II. *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

Table II 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).

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, $p = 0.58$; comparison subjects: 12.1 (1.7)% and 13.1 (1.7)%, respectively, $p = 0.31$). Therefore, the data from the AM measurements were averaged over the 2 consecutive days (Table III). None of the outcome measures between the 2 groups reached statistical significance. There was a trend ($p = 0.07$) 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 8 liver transplant recipients were classified as hypoactive (i.e. the 2 persons with acute liver failure and 3 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 ($r_s = -0.81$, $p = 0.01$ and $r_s = -0.84$, $p = 0.01$, respectively; Fig. 1).

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

At the $p = 0.10$ level, time post-transplantation was inversely correlated with mean motility ($r_s = -0.64$, $p = 0.09$) (Fig. 2). The relationship between time post-transplantation and duration of dynamic activities was not significant ($r_s = -0.61$, $p = 0.11$).

Table IV 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 ($p \leq 0.05$ and $p \leq 0.10$).

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, 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 I). 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 2 groups (2 liver transplant recipients had physically active jobs, whereas all employed comparison subjects had physically passive jobs) to seriously affect the main findings.

Table III. *Everyday physical activity as measured with the Activity Monitor in 8 liver transplant recipients and 8 comparison subjects. Data are calculated per day and are presented as mean (SD) over the 2 measurement days.*

	Liver recipients ($n = 8$)	Comparison subjects ($n = 8$)
Duration of dynamic activities (%)*	10.2 (3.8)	12.6 (0.9)
Mean motility (g)†	0.023 (0.007)	0.029 (0.007)
Motility during walking (g)‡	0.164 (0.015)	0.172 (0.024)
Transitions (number) §	119 (26)	121 (26)
Walking periods >10 seconds (number)	155 (54)	197 (35)#

#$p < 0.10$ (trend).
*Composite measure (walking, cycling, general movement) expressed as percentage of a 24-hour period.
†Intensity of everyday physical activity (1 g = 9.81 m/s^2).
‡Walking speed.
§Contains all transitions except the lying transitions such as the transition from lying prone to lying supine.

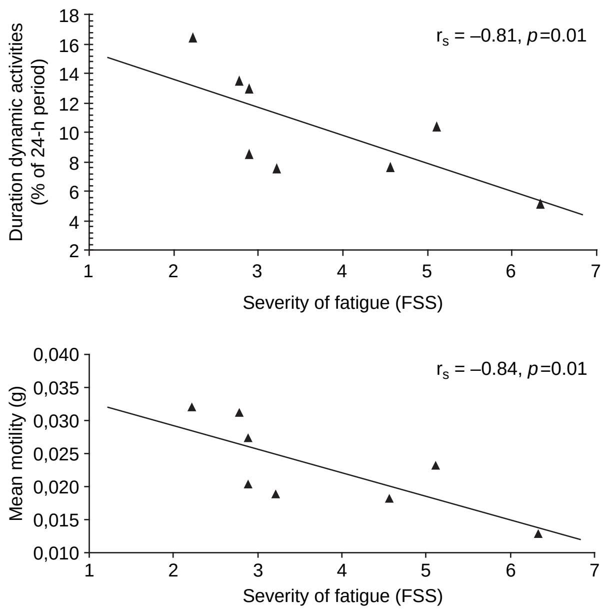

Fig. 1. Correlations between severity of fatigue on the one hand and duration of dynamic activities and mean motility on the other in 8 liver transplant recipients. Mean motility represents intensity of everyday physical activity (1 g = 9.81 m/s^2).

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 (11–13). 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 to the composition of the study sample. Because we wanted to obtain an insight into the relationship between severity of fatigue and the level of everyday physical activity, liver transplant recipients with no signs of fatigue were also included. Based on the inverse relationship that we found between severity of fatigue and level of everyday physical activity, we expect that if more severely fatigued liver transplant recipients were included in the present study, activity levels would have been found to be significantly lower in the patients than in their healthy comparison subjects.

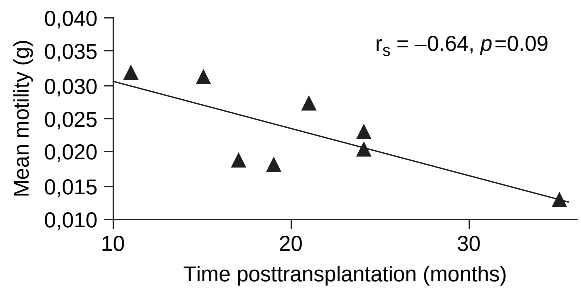

Fig. 2. Relation between time post-transplantation and mean motility in 8 liver transplant recipients. Mean motility represents intensity of everyday physical activity (1 g = 9.81 m/s^2).

Although this cross-sectional study does not allow us to conclude that fatigue results in a hypoactive lifestyle (or vice versa), there may be an interaction between the 2 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 those with a chronic cause for liver transplantation, because no period of deconditioning has preceded the transplantation. However, in the

Table IV. *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 and mean motility on the other in 8 liver transplant recipients*

	Scores on Rand-36	Relation with duration dynamic activities	Relation with mean motility
RAND-36 domain	Mean (SD)	r_s	r_s
Physical function	86.3 (11.6)	0.72*	0.75*
Social functioning	73.3 (22.8)	0.35	0.48
Role-Physical	59.4 (35.2)	0.25	0.38
Role-Emotional	75.0 (46.3)	0.63#	0.76*
Mental health	78.0 (15.9)	0.72*	0.78*
Vitality	68.8 (18.1)	0.46	0.59
Bodily pain	76.8 (29.0)	0.38	0.50
General health	56.9 (8.0)	0.68	0.72
Changes in health	81.3 (22.2)	0.21	0.21

Results are mean (SD) or Spearman correlation coefficients (r_s). Duration dynamic activities: composite measure (walking, cycling, general movement) expressed as percentage of a 24-hour period, Mean motility: represents intensity of everyday physical activity (1 g = 9.81 m/s^2); *$p \leq 0.05$, $^{\#}p < 0.10$ (trend).

present study, the 2 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 (unpublished observation; principal author).

Results of the present study seem to be in contrast to those of Nicholas et al. (19) 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 vs accelerometry-based AM; sports participation vs everyday physical activity) and differences in time post-transplantation. The study of Nicholas et al. (19) also included persons more than 3 years after liver transplantation, whereas the post-transplantation period in the present study ranged from 6 months to 3 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 ($p = 0.10$ level, Fig. 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 (unpublished observation; principal author). 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 (18), 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 1–3 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 IV) seem to confirm the Surgeon General's Report on physical activity and health status (20) 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". Although different aspects of everyday physical activity were measured, Painter et al. (21) also found that physical activity is related to HRQoL after liver transplantation. They measured participation in regular physical activity in 180 persons 5 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 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, 5 of the 8 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 to 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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