A Web-based exercise intervention for effective complementary treatment of patients with NAFLD - First results of the HELP-Study

Pfirrmann, D.1, Huber, Y.2, Schattenberg JM.2, Simon P.1

1Institute of Sports Science, Department of Sports Medicine, Johannes Gutenberg University
2University Medical Center of the Johannes Gutenberg University, Department of Internal Medicine

Abstract

Background

Physical inactivity is a major risk factor for non-alcoholic fatty liver disease (NAFLD). Improvement of cardiorespiratory fitness (CRF) by exercise based prevention interventions is a recommended complementary treatment for NAFLD. Enabling patients to achieve minimally effective physical activity recommendations to improve CRF, typically requires high personal and financial expenses in face-to-face settings. Here we designed an eHealth approach for patients with NAFLD to overcome typical intrinsic and extrinsic barriers for the improvement of CRF (HELP-Study).

Objective

We assessed the effectiveness of an 8-week tailored Web-based exercise intervention for the improvement of CRF, expressed as \( \text{VO}_{2\text{peak}} \), in patients with histologically confirmed NAFLD.

Methods

In a 24-month period, 44 patients were enrolled into an 8-week prospective, single-arm study. After a medical examination and performance diagnostics, a sports therapist introduced the patients to a Web-based platform for individualized training support. Regular individual patient feedback, was used to systematically adapt the weekly exercise schedule. This enabled to monitor and warrant patient adherence to strength and endurance training and to optimize the step-wise progressive exercise load. Exercise progression was based on an a priori algorithm taking the subjective rate for both, perceived exhaustion and general physical discomfort into account. \( \text{VO}_{2\text{peak}} \) was assessed at baseline and at the end of the study by spiroergometry.
Results

Forty-three patients completed the intervention with no adverse events reported. VO\textsubscript{2peak} significantly increased 8.5 % by 2.4 ml/kg/min (95% CI: 1.48 - 3.27, \(P < .0001\)) accompanied by a 1.0 kg (95% CI: 320.33 – 1.58, \(P = .004\)) body weight reduction and a 1.3 kg (95% CI: 0.27 – 2.27, \(P = .01\)) body fat mass reduction. In an exploratory analysis step-wise logistic regression analysis revealed low body fat and low VO\textsubscript{2peak} at baseline as well as the total minutes of endurance training during the intervention as main contributors to a positive change in VO\textsubscript{2peak}. Our predictive model indicated that the average NAFLD patient needed 223 min for stabilization of VO\textsubscript{2peak}, while 628 min were required to achieve average improvement in VO\textsubscript{2peak}. However, in patients with a roughly 20 % higher than average VO\textsubscript{2peak} these 628 min were only sufficient to stabilize VO\textsubscript{2peak} and a more than 40 % lower than average fat mass would be required for such subjects with high VO\textsubscript{2peak} to achieve an average outcome.

Conclusions

Here we show for the first time that patients with NAFLD can be effectively supported by a Web-based approach enabling similar increases in VO\textsubscript{2peak} as face-to-face interventions. Patients with low body fat and low VO\textsubscript{2peak} turned out to profit the most from our intervention. In terms of future treatment strategies, this implies that NAFLD patients with high body fat may particularly benefit from body fat reduction by a sharp nutritional intervention in first place thus enabling a more effective exercise intervention, subsequently.

Trial Registration: Clinicaltrials.gov: NCT02526732


Keywords: Web-based, exercise, NAFLD, fatty liver, treatment, lifestyle

Introduction
Sedentary behavior and an unhealthy diet are common in Western industrialized countries [1, 2]. Modern lifestyle increases the risk for chronic diseases such as the metabolic syndrome [2-5]. In accordance to the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in adults, the metabolic syndrome is defined by the presence of abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, and impaired fasting glycaemia [6]. In the last years, the nonalcoholic fatty liver disease (NAFLD) has been moving into the spotlight, since it has the highest increase in the incidence among chronic liver diseases worldwide [3, 654, 7-9]. Some researchers describe NAFLD as a part (hepatic manifestation of metabolic syndrome) or at least a partial result of the metabolic syndrome [3, 10-13]. Independent of age or ethnicity, 20 to 6730% show fatty changes in the liver with an increasing tendency [8, 11, 14-17] and the prevalence is still higher in patients with diabetes [18]. NAFLD is seen as a benign preliminary stage with the potential to progress: from simple steatosis towards non-alcoholic steatohepatitis (NASH), cirrhosis and finally hepatocellular carcinoma (HCC) [9, 19-22]. The pathways driving this progression are numerous and complex, [22, 23] and not every patient with NAFLD develops cirrhosis related complications [9, 24]. However, patients have a higher mortality rate, when compared to the general population [9, 24, 25]. Most of patients with NAFLD are asymptomatic [16, 19, 26]. Some suffer from unspecific symptoms, such as fatigue [26, 27] and depression [28], which additionally affects the health related quality of life (HRQOL) [29, 30]. If left untreated, most patients will develop diabetes as a long-term result [9]. In order to improve the condition of the liver and to reduce additional risk factors, changes towards a balanced nutrition and a more physically active lifestyle are recommended in daily life [21, 26, 31-34]. The Practice Guideline by the American Association for the Study of Liver Diseases (AASLD) recommend a loss of at least 3-5% of body weight, in order to improve steatosis. Current recommendation for adult patients with NAFLD or NASH is a physical activity target of at least 150 minutes exercise per week of moderate intensity or at least 75 minutes per week of vigorous intensity [36]. In addition strengthening exercises should be performed twice a week [36]. Most people with NAFLD do not know about the presence of the disease, because of the absence of any specific symptom. Therefore, NAFLD is occasionally self-caused [37], and develops and progresses over years. Studies showed a reduced physical activity level (intensity and amount) in patients with NAFLD compared to healthy individuals [12, 27, 38] and a suboptimal cardiorespiratory fitness with fewer than 20% of patients meeting recommended physical activity guidelines [39]. In a survey conducted by Kistler, 54% mentioned to be inactive, while 57% of them reported no recreational activity. The remaining 43% stated some activity, which was, however, not enough to achieve the goals set in the recommendations [40]. Besides the decreased activity level, prolonged sitting time is associated with a higher prevalence of NAFLD [41, 42]. At the point of diagnosis, patients are encouraged to immediately change many aspects in their daily routine. Here, different barriers and
Obstacles have to be overcome. Time and place constraints, for instance, are common problems for a regular activity [4, 37, 43, 44]. Changing one’s lifestyle is not easy, especially for patients with highly sedentary habits [45]. Consequently, regular motivational support from experts is needed [45]. Thus, advances in modern technologies should be taken into account for promoting health-conscious behavior [43]. In a survey conducted by Pew Research Center in 2015, 84% of American adults have access to a computer and regularly use the internet [46]. In 2005, 75% of internet users searched for health information and 42% of them searched for specific information about exercise and training [47]. The possibility to reach and support large numbers of patients via the internet [48] can thus be seen as a cost-effective possibility to improve and maintain an active lifestyle [49]. Web-based interventions with cancer patients produced first promising results [50, 51]. The aim of our prospective, non-randomized pilot study, was to find out, whether online support aids patients with NAFLD or NASH in establishing and maintaining a regular level of physical activity and whether the individualized training recommendations improve the overall physical fitness determined as VO$_{2\text{peak}}$ and body composition.

Methods

The HELP study is a prospective, single arm study in patients with histologically confirmed NAFLD and NAFLD and explored the feasibility and effectivity of an individualized exercise intervention. A total of 46 patients were recruited from August 2015 to December 2017. The study was registered at (clinicaltrials.gov NCT02526732).

Patient Selection

Inclusion criteria were (1) age between 18 and 70; (2) histologically proven NAFLD. Subjects were excluded if they had (1) bariatric operation in the past five years; (2) body mass index (BMI) below 18.5 kg/m$^2$ or higher than 45 kg/m$^2$; (3) instable coronary heart disease; (4) coronary interventions in the past six months; (5) stroke in the past six months; (6) higher grade of coronary artery disease (II-IV); (7) chronic obstructive pulmonary disease (COPD); (8) renal or metabolic abnormalities; (9) uncontrolled hypertension; (10) presence of other liver diseases, such as hepatitis; (11) presence of decompensated liver cirrhosis; (12) presence of HCC; (13) alcohol consumption >30g / day in men and >20g / day in women; (14) pregnancy; (15) medications that can cause secondary NASH (for example corticosteroids); (16) presence of other immunological or inflammatory diseases (e.g. systemic lupus erythematosus (SLE)); (17) musculoskeletal disorders; (18) Marcumar therapy.

The primary outcome was defined as a change in VO$_{2\text{peak}}$ from the baseline. The secondary outcome measures included changes in body composition, and feasibility as well as safety of the Web-based
Assessment of the outcome was performed before and after the 8-week intervention, as described.

**Clinical examination**
All eligible patients were screened and recruited at the outpatient hepatology clinic of the University Medical Center Mainz.

**Sports medical examination**
After informed consent, patients underwent clinical examination and were referred for a cardiopulmonary exercise test until exhaustion at the Department of Sports Medicine, University Mainz. A standard 12-lead resting electrocardiogram (ECG) and a pulmonary function test (Spirometry); (Body Box 5500, Medisoft) were performed. In addition, the body composition was measured by Bio-Impedance Analysis (BIA), (InBody 3.0, Biospace). After the exercise test each patient was registered and trained by the administrator on the webpage. In addition to a detailed explanation, a manual for the homepage, a heart rate monitor and three elastic tapes were provided. For more detailed information on study flow, a video clip is available. (see Multimedia Appendix 1).

**Cardiopulmonary exercise test**
All study participants performed a stepwise exercise test on a treadmill until volitional exhaustion (subjective) or until meeting an objective criterion (i.e. inappropriate blood pressure response or changes in ECG). Each stage of the modified walking protocol lasted for 3 minutes and intensity was increased by speed and elevation of the treadmill (Saturn, HP Cosmos) [52]. Continuous expired gas analysis (breath by breath) was performed (Ergostik, Geratherm) and heart rate was monitored during the test. Blood samples from the earlobe were taken at the end of each stage to determine lactate concentration and blood pressure was measured in every second stage. The subjective condition was measured utilizing the BORG scale (6-20) 30 seconds before the end of each stage.

**Follow-up assessment**
All participants performed the clinical and sports medical examination described above at study start and again after eight weeks. The clinical examination was additionally performed 12 weeks after the end of the intervention (Fig. 1).
Patients received exercise recommendations via system internal messages on a weekly basis [53]. Depending on the initial exercise test and the subjective feedback from the patients during the intervention period of eight weeks, the exercise program was adjusted for each patient. In order to avoid early dropouts, moderate exercise intensity with three sessions per week was chosen (2x endurance training (walking/running) and 1x strength training (major muscle groups)). The program was intensified after a four-week familiarization to reach a frequency of five sessions per week (3x endurance training and 2x strength training) for the remaining four weeks. Beside the frequent interaction with a counselor, peer support is considered as a cornerstone in the concept. Therefore, a discussion board and a chatroom were implemented, in order to improve social support and adherence [54].

**Strength training**
A program of ten strength exercises should be carried out in a prescribed sequence, to stimulate muscular strength in the major muscle groups. A detailed, illustrated instruction and video files for the exercises were available on the website. Training individualization was achieved by varying the number of repetitions or number of sets.

**Endurance training**
The individualized endurance training was based on lactate measurements. The intensity of the jogging program was controlled by a heart rate (HR) measurement (FT1, Polar). After an initial continuous method with a HR at the lactate threshold (LT), the training followed the interval method (e.g. 2 x 4 min, 2 x 3 min, 2 x 2min with 2 min. at rest) at a higher HR. The intensity of training was achieved by adjusting the interval time or by adding additional intervals.
Training process

Endurance training and strength training, consisting of bodyweight exercises and exercises with elastic tapes, were the main content of the training recommendations. Each training started with a 5-180-minute warm-up and was followed by a 5-minute cool-down phase. A selection of relaxation and breathing exercises were also available on the website. At the end of each week, the patients sent in a filled schedule with important information such as average heart rate, resting heart rate, and training time. In addition, two values were asked to allow the modification the training intensity and duration for the following week. First, the patient’s individual assessment of pain and assessment of training load was determined as modified BORG value (1-10), after each training session. Second, a traffic light principle was used to regulate the intensity of the next week’s training. Depending on the individual feedback an increase or decrease of the training recommendations were possible, whereby the pain value was dominant for the decision [53]. The weekly feedback should ensure an appropriate load according to individual abilities and assess the compliance. In addition, a group training was offered biweekly at the sports center of the University Mainz.

Statistical Procedures

Statistical analysis was performed by using SPSS Statistics version 23 and JMP. Descriptive statistics were used for the presentation of baseline characteristics and the using behavior of the website. Variables were described by using mean, median, and standard deviation (SD). Normal distribution was tested with Shapiro-Wilk-Test due to the small sample size. In case of normal distribution, the paired students t-test was used in order to determine within group differences before and after eight weeks’ intervention. Intention to treat analysis was performed and the data were processed according to the last observation carried forward method. A P-value of P < .05 was considered statistically significant. For the investigation of the factors that contribute to changes in VO\(_{2\text{peak}}\), we employed a two-step procedure. Fold-Change in VO\(_{2\text{peak}}\) had to be normalized by a normalization procedure using the inverse of the squared values, as suggested by box-cox analysis. First, we computed a step-wise feed-forward logistic regression analysis. In order to warrant stringent inclusion criteria, we fed the model on the one hand with the baseline data on anthropometrics including body composition and performance data, as presented in Table 1, and with the data on endurance training (for the 8 weeks) and the total exercise time (strength and endurance training in minutes for 8 weeks). Only 3 factors emerged that reached a significance level set at .05 for entering a single variable into the regression equation. These factors were used to compute a logistic regression analysis.
Results

Baseline characteristics

46 patients were screened and after exclusion of two patients were 44 patients included in the study (see Fig. 2). One patient dropped out (2.3 %) during the intervention period.

Among patients, three (6.8 %) had a normal weight status, 15 (34.1 %) were overweight, and 26 (59.1 %) were obese. Characteristics at study start are summarized in Table 1. 30 patients (68.2 %) were male, with a mean age of 42 years. 41 (93.2 %) had a BMI above 25 and more than 27 % percent of body fat. In total, 1166 exercise recommendations (729 endurance; 437 strength) were performed and 222 recommended workouts were cancelled due to different reasons.

Table 1 Baseline characteristics of patients enrolled in the HELP study

<table>
<thead>
<tr>
<th>characteristics (N: 44)</th>
<th>value</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (y)</td>
<td>42.0 (SD 10.9)</td>
</tr>
<tr>
<td>&lt; 30 years</td>
<td>5 (11.4%)</td>
</tr>
<tr>
<td>30-60 years</td>
<td>38 (86.4%)</td>
</tr>
<tr>
<td>&gt; 60 years</td>
<td>1 (2.3%)</td>
</tr>
<tr>
<td>male, n (%)</td>
<td>30 (68.2%)</td>
</tr>
<tr>
<td>height (cm)</td>
<td>175 (SD 10.3)</td>
</tr>
<tr>
<td>weight (kg)</td>
<td>95.9 (SD 17.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.2 (SD 4.3)</td>
</tr>
<tr>
<td>overweight (BMI &gt; 25 &lt; 30)</td>
<td>15 (34.1%)</td>
</tr>
<tr>
<td>obese (BMI &gt; 30)</td>
<td>26 (59.1%)</td>
</tr>
<tr>
<td>body composition</td>
<td></td>
</tr>
<tr>
<td>body fat (kg)</td>
<td>26.7 (SD 8.2)</td>
</tr>
<tr>
<td>body fat (%)</td>
<td></td>
</tr>
</tbody>
</table>
Primary Outcome

At baseline, the mean VO$_{2\text{peak}}$ was 27.2 ml/kg/min. After eight weeks of intervention, the VO$_{2\text{peak}}$ significantly increased by 8.8% (from 27.2 ml/kg/min (SD 5.1) to 29.6 ml/kg/min (SD 5.4); (95% CI: 233-3.27 – -1.48, P < .0001); (Fig. 3).

We employed logistic regression analysis to assess the combined effects of the variables shown in Table 1 on the fold-change in VO$_{2\text{max}}$ by step-wise feed-forward logistic regression analysis. A multiple linear regression model with three independent predictors emerged based on a total of 43 observations (df =3; F = 8.03, r$^2$ = 0.38; P < .001). All predictors had a significant influence and a
249Corrected power of more than 80% with VO peak at baseline (t = -3.77; std. effect size = -0.12; 95% CI: 250-0.18 - 0.05; P < .001, total minutes of endurance training during the intervention period of eight 251weeks (t = 3.27; std. effect size = 0.09; 95% CI: 0.04 - 0.15; P = .002), and body fat (%) at baseline (t = 252-3.22 std. effect size = -0.10; 95% CI:-0.17 - -0.04; P = .003). The model indicated that participants 253in the program with average body fat percentage (27.9 %) and average VO peak at baseline (27.1 254ml/kg/min) would need roughly 223 hours of training within the intervention period to maintain their 255baseline VO peak (Fig. 4a), while 628 hours of training are required to reach the average improvement 256of basal VO peak of roughly 8 % (Fig. 4b). However, a high VO peak at baseline with average fat mass 257would lead to a significantly lower outcome (Fig. 4c) that can principally be compensated, if 258candidates with higher baseline VO peak also have a lower fat mass (Fig. 4d).

Figure 4 Predictive analysis for fold-change (FC) in VO max. The linear effect of VO peak at study start, total minutes of 260endurance training during the intervention period of eight weeks and body fat in percent at study start is presented as solid 261black regression lines and dashed blue lines indicate the respective upper and lower 95% CIs for the regressions. (a) 262According to this model 222 minutes endurance training are needed to stabilize VO max in the collective for a person with 263average VO peak of 27 ml/kg/min and average body fat of 27.9 %. (b) For an improvement of roughly 8 % VO max, an endurance 264training load of at least 600 minutes over eight weeks is necessary. (c) A higher initial VO peak leads to a reduced effect of the 265628 minutes endurance training within eight weeks on the primary outcome VO max. (d) In principal, a lower body fat (%) 266could compensate for the higher VO peak at baseline (33.67) and still enable an eight percent improvement in VO max, with the 267same training load.

Secondary Outcomes

279Significant changes could be observed in body weight and Body Mass Index (BMI) (95% CI: 0.33 – 2801.58, P = .004), (95% CI: 0.14 – 0.54, P = .001) respectively. With regard to the body composition, 282there is a significant reduction in body fat (95% CI: 0.27 – 2.27, P = .01) and thus the percentage of 283body fat (95% CI: 0.26 – 2.11, P = .01) and a slight, but not significant increase in lean body mass (Tab.
2842). There is a trend towards a lower resting heart rate (95% CI: -0.18 – 7.22, \( P = .06 \)) and no changes in lung function expressed as FEV1 (95% CI: -4.11 – 1.38, \( P = .32 \)) and vital capacity (95% CI: -1.09 – 3.41, \( P = .31 \)) could be observed.

**Table 2 study results**

<table>
<thead>
<tr>
<th>characteristics (n:44)</th>
<th>pre</th>
<th>post</th>
<th>Difference (%)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight (kg)</td>
<td>95.9 (SD 17.4)</td>
<td>95.0 (SD 17.8)</td>
<td>0.9 (0.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.2 (SD 4.3)</td>
<td>30.8 (SD 4.4)</td>
<td>0.4 (1.3)</td>
<td>0.001</td>
</tr>
<tr>
<td>overweight (BMI &gt; 25 &lt; 30) (%)</td>
<td>15 (34.1)</td>
<td>14 (32.6)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>obese (BMI &gt; 30) (%)</td>
<td>26 (59.1)</td>
<td>26 (59.1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>body composition</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>body fat (kg)</td>
<td>26.7 (SD 8.2)</td>
<td>25.5 (SD 9.0)</td>
<td>1.2 (4.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>body fat (%)</td>
<td>27.9 (SD 7.4)</td>
<td>26.8 (SD 8.4)</td>
<td>1.1 (3.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>lean body mass (kg)</td>
<td>64.8 (SD 14.1)</td>
<td>65.2 (SD 14.2)</td>
<td>0.4 (0.6)</td>
<td>0.31</td>
</tr>
<tr>
<td>spirometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>forced vital capacity (FVC) (%norm)</td>
<td>107.5 (SD 13.3)</td>
<td>106.3 (SD 14.2)</td>
<td>1.2 (1.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>forced expiratory volume (FEV1) (%norm)</td>
<td>96.3 (SD 16.3)</td>
<td>97.6 (SD 13.3)</td>
<td>1.3 (1.3)</td>
<td>0.32</td>
</tr>
<tr>
<td>spiroergometry</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>resting heart rate (bpm)</td>
<td>79 (SD 10.2)</td>
<td>75 (SD 11.5)</td>
<td>4 (5)</td>
<td>0.06</td>
</tr>
<tr>
<td>( VO_2 \text{peak} ) (ml/kg/min)</td>
<td>27.2 (SD 6.1)</td>
<td>29.6 (SD 5.4)</td>
<td>2.4 (8.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>watt max</td>
<td>135.1 (SD 42.9)</td>
<td>149.5 (SD 49.5)</td>
<td>14.4 (10.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>watt IAT</td>
<td>96.1 (SD 21.5)</td>
<td>100.6 (SD 24.6)</td>
<td>4.5 (4.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>BORG value max (6-20)</td>
<td>18.5 (1.5)</td>
<td>18 (1.8)</td>
<td>0.5 (2.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>heart frequency (HF max)</td>
<td>172 (SD 16)</td>
<td>172 (SD 14.8)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Further, significant changes in the power, expressed as Watt max (95% CI: -18.46 – -10.17, \( P < .001 \)), and Watt at the individual anaerobic threshold (IAT) (95% CI: -7.00 – -2.05, \( P = .001 \)) were observed (Fig. 5). The maximum heart frequency remains unchanged and the subjective perception of exhaustion, expressed as BORG-value, decreased significantly from baseline to post intervention (95% CI: -0.05 – 0.95, \( P = .02 \)), as shown in Table 2.
Figure 5. Fold changes for maximum Watt, VO2max, body fat, and Watt at the individual anaerobic threshold.

Website Use

All study participants were registered on the homepage at study start. The registration- and explanation process took about one hour and was integrated between the end of the treadmill test and the last blood sampling at 90 minutes post-test. During the intervention period, regular communication and feedback were easily achieved using the webpage. In some cases, the patients did not send the exercise feedback on time. Therefore, 120 reminders were sent in total to the participants in order to ask for the exercise feedback. The average user behavior in terms of log-in duration and frequency is presented in Table 3. The participants’ average length of a visit was about 12 minutes and the average log-in frequency was 13 times during the intervention period of eight weeks.

Table 3 Using behavior of the homepage during the intervention period of eight weeks.

<table>
<thead>
<tr>
<th>characteristics (N:43)</th>
<th>total number of log-ins (sum; mean)</th>
<th>557 (13.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>total log-in duration in minutes (sum; mean)</td>
<td>6548 (152.3)</td>
<td></td>
</tr>
<tr>
<td>reminder (sum; mean)</td>
<td>120 (2.8)</td>
<td></td>
</tr>
<tr>
<td>using e-mail instead of the website for exercise feedback (sum; mean)</td>
<td>165 (3.8)</td>
<td></td>
</tr>
</tbody>
</table>

However, there is a descending trend in registration frequency and duration over time, as shown in Figure 6 and 7. Nevertheless, a timely response was still achieved, also in patients who did not continue to use the webpage, by interacting via conventional e-mail (Tab. 3).
As illustrated in Figure 8, the physical activity level increased steadily over the period of eight weeks. After an initial familiarization period, the exercise recommendations increased progressively. In the second half of the intervention, the patients reached and exceeded the recommended activity goal of the world health organization (WHO) [55]. The study participants performed 72 additional workouts (e.g. hiking, playing volleyball or badminton) (Tab. 4). However, the participants were not obliged to record other leisure time activities, and therefore the additional exercises were not further examined. The adherence to the Web-based exercise concept, expressed as 80% or more of the endurance workouts, was pretty good. 33 participants (77%) performed 80% or more of the recommended endurance workouts. Common reasons for breaks were due to deadlines (e.g. congress participation, workshops), medical reasons (e.g. cold, inflammation, blisters, headache, or food poisoning), external conditions (e.g. high temperature or heavy rain), or private reasons. In total 222 exercise recommendations were not performed as recommended (Tab. 4).
Figure 8 Development of the physical activity level, expressed as weekly endurance training in minutes. The dashed line indicates the recommended vigorous activity goal of 75 minutes per week from the WHO.

Table 4 Presentation of the exercise profile

<table>
<thead>
<tr>
<th>characteristics (N:43)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>total physical activity within eight weeks</td>
<td>52373 (1218)</td>
</tr>
<tr>
<td>in minutes (sum; mean)</td>
<td></td>
</tr>
<tr>
<td>endurance training within eight weeks</td>
<td>29104 (677)</td>
</tr>
<tr>
<td>in minutes (sum; mean)</td>
<td></td>
</tr>
<tr>
<td>interruption of exercise training (sum; mean)</td>
<td>222 (5)</td>
</tr>
<tr>
<td>additional workouts (sum; mean)</td>
<td>72 (1.7)</td>
</tr>
</tbody>
</table>

Adverse events

The online exercise concept was well-accepted by the patients. The intervention in this group of patients with liver disease was safe. No serious adverse events occurred during the study period.

Discussion

Current guidelines recommend lifestyle changes as the primary approach to treat obesity and NAFLD, however few studies, focusing on physical activity, have been published. Neither the type nor the intensity of exercise has been defined. Also, it has been suggested that physical deconditioning of patients with NAFLD leads to the inability to adhere to exercise recommendations. The HELP study explored the feasibility and the efficiency of a Web-based and patient-centered exercise support concept.

The role of weight loss

Weight loss is a major topic in the treatment of NAFLD [56]. The guidelines and experts in field recommend a weight loss of at least 3-5 % to improve steatosis [35, 57]. Anyway, there are critical
limits mentioned, below the weight loss must not fall. A weight loss of 1.6 kg per week should not be exceeded due to potentially provoked portal inflammation or portal fibrosis. Furthermore, three study participants in this investigation showed a normal weight status and a weight reduction is therefore not needed. The term weight management is more accurate instead of weight loss. We were able to show a significant but extremely low weight change, and this is in accordance to other exercise studies. Weight gain is a result of a higher energy intake and a reduced energy expenditure. Weight reduction is only possible if the energy expenditure persistently exceeds the energy intake. Therefore, diet is a necessary aspect in weight reduction. Furthermore, with reference to the above described prediction model (Fig. 4), the reduction of the fat mass percentage is crucial in order to significantly improve the cardiorespiratory fitness with an achievable amount of physical activity. Regular exercise supports energy expenditure, but conscious nutrition is essential for energy intake control. Furthermore, the absence of weight loss might partly be explained by a moderate shift from fat mass to fat free mass. Regular activity reduces body fat, however, lean body mass increases. Another explanation for not observing a weight loss during the intervention is an insufficient negative energy balance due to a low starting intensity. For an effective weight loss, a longer duration and accordingly an increased intensity is required.

Nevertheless, exercise studies show, irrespective of nutrition, promising results in terms of decreased insulin and homeostasis model assessment index (HOMA-IR), improved cardiorespiratory fitness, reduced hepatic and visceral lipids, reduced liver enzymes and modulated liver fat. Exercise combined with an adjusted diet shows strong interaction effects in relation to weight change, but exercise has also independent modes of action. Thus, physical activity or structured exercise recommendations should be strongly promoted due to additional benefits in the absence of a weight loss.

The improvement of the fitness

In the short intervention period of eight weeks, the results of this study are comparable to those of face to face interventions, with respect to changes in body composition and peak exercise capacity. Takahashi (2015) already assessed the efficiency and safety of two simple resistance exercises in 53 patients with NAFLD. After a 12-week period, patients in the intervention group had a significantly increased mean level of fat-free mass (-0.24 ± 0.88 vs. 0.30 ± 0.67 kg, \(P = .01\)) and muscle mass (-0.24 ± 0.82 vs. 0.25 ± 0.70 kg, \(P = .02\)) compared to the control group. This changes are similar to our findings. Further, a change of nearly 9% in VO\(_{2}\text{peak}\) could be also shown in an investigation by Sullivan. Participants in the intervention group trained five times per week for 16 weeks. The subjects exercised under supervision once a week, and were encouraged to perform the remaining four sessions in their home environment. The endurance training was controlled by heart rate measurement. In our study a combination of the heart rate, as objective measure and the Borg
value [69] as subjective measure were used for the determination of the intensity. Borg values are considered as an appropriate measure for monitoring and regulating exercise intensity [34, 70, 71]. To clarify whether the intensity or the volume is more effective, Keating (2015) aimed to determine the more important training parameter in inactive overweight adults [61]. 47 obese adults trained for eight weeks either with low intensity and high volume (LO:HI), or high intensity and low volume (HI:LO), or low intensity and low volume (LO:LO), or were prescribed a stretching and self-massage program (placebo = PLA). The investigators came to the conclusion, that volume as well as intensity were both efficient [61]. However, with a view to adherence, an investigation by Perri found out, that a higher exercise frequency is more accepted, compared to a higher exercise intensity [72]. Furthermore, high exercise intensity conditions resulted in a higher percentage of exercise-related injuries [72]. Beside the positive effects of regular physical activity, independent of intensity and volume, the most important challenge is, to face the adherence to exercise [73].

The importance of regular support

It is recommended to be physically active on five days a week. In addition a resistance training on at least two days a week should be performed. In contrast to the findings of Perri, [72] many study participants in this trial reported at the end of the study, that they struggled with the integration of the demanding volume in the second half of the intervention. Berzagotti (2016) summarized the beneficial effects of exercise on the health of NAFLD patients, but also discuss high dropout rates in physical activity trials in these patients [3]. There is an urgent need to counteract with the sedentary habits of NAFLD patients. Besides all the proven positive effects of regular physical activity and a healthy diet, many people are still lacking in long-term motivation [74]. Engaging in less physical activity increases the risk of fatty changes in the liver [41, 75, 76]. In the investigation of Hsieh (1998), the physical inactive group showed a significantly higher prevalence of fatty liver changes [76]. This statement is supported by the results of a study by Perseghin (2007). They showed an association between habitual physical activity and intrahepatic fat content [77]. Furthermore, a large cross sectional study by Ryu (2015) fully supports this statement, that prolonged sitting times are positively associated with the prevalence of NAFLD [42]. Therefore, supporting patients to achieve and sustain regular activity is a key issue in NAFLD management [12]. Due to the pronounced sedentary lifestyle, starting with a low training volume and intensity is indicated because of motivational reasons. Self-chosen sitting times should be reduced and barriers for regular exercise should be identified and eliminated [78]. Intensive exercise interventions, carried out under supervision in hospitals or fitness centers, [32, 34, 65, 67] impose an unnatural lifestyle on the patients for a short period of time. After the intervention, patients very quickly lose motivation and fall back into their old habits [45]. There is a strong need and a high potential for Web-based intervention designs [79, 80]. Web-based interventions are essential to bridge the treatment gap between demand and supply [81, 82].
study conducted by Casey, patients with diabetes stated that they need a better transition strategy to subsequent post-intervention realities of less support [83]. Furthermore, from the patient’s point of view, scheduling flexibility and geographical proximity are important factors that should be taken into account [83]. Even the most powerful individualized exercise program enhances the patient’s situation sustainably only, if patients are able to transfer the regular activity into their daily routine [84]. Therefore, the main focus is to incorporate an exercise program into the daily routine of NALFD patients to promote long-term changes [85] and reverse sedentariness [86]. Regular feedback from a counselor seems to be an important aspect for patients to stay motivated [87, 88]. Furthermore, it is important to integrate the patient in the decision process [84]. Thus, a change from compliance (implementation of prescription) to adherence (mutual agreement between patient and caregiver) should be achieved [80, 84]. Growing interest in utilization of modern technologies such as computer and smartphone could for this purpose represent feasible ways to transport knowledge and care in a home-based setting. Web-based support allows a flexible scheduling of training and still transport proper guidance through regular counseling and tailored feedback. In the study presented here, common obstacles like time constraints (e.g. shift work or family responsibilities) or no access to a fitness center (e.g. distance, high costs, or lack of sound advice) [37, 43, 45] could be circumvented using additional training equipment like pulse watches and elastic bands. Furthermore, a regular, close communication with a team of experts was realized by the communication via the specially designed website. This approach reduced the mentioned geographical and time-related barriers. In contrast to print-based interventions and face-to-face counseling, the Web-based communication lowers costs and has a higher potential to reach a wide range of target groups with tailored support [43, 49, 89]. Individualized recommendations based on heart frequency and personal feedback, expressed as RPE values seem to be useful in this context [34].

The present trial is one of the first to test the feasibility of a Web-based exercise program in a group of patients with liver disease. In line with the recommendations of current guidelines, this is also one of the first investigations supporting patients with NAFLD with a combined endurance and strength training concept.

Strengths and limitations

This study has several strengths and limitations. Strengths of this study could be seen in the liver biopsy which is the gold standard in determining liver condition [7, 90]. Furthermore, we are the first to conduct a Web-based approach for a tailored exercise intervention in this patient collective. In contrast to other studies, we had only one (2.3 %) dropout, showing good adherence and tolerance, whereas in a recent review the dropout rates ranged between 6 % and 45 % with similar intervention content [73]. Possible advantages of the Web-based approach are the flexible design and the exercise implementation in the home environment. The main limitation is, that investigators had to rely at
least partially on subjective feedback for training adherence without the possibility of a visual control by the sports physician. Data on training adherence might be prone to social desirability bias as well as over- or underestimation. Researchers already discussed this issue of over- or underestimation in home-based training settings [91, 92]. To reduce such potential bias, we combined the subjective feedback (Borg rating for training sessions) with an objective measurement (average heart rate). A person that tended to respond in a socially desirable fashion would at least need some in-depth knowledge in exercise physiology to trick the therapist or would most likely submit non-plausible data. Another aspect to be considered is the absence of a control group. Because of different comorbidities, some patients had to be excluded. Therefore, we do probably not present a typical NAFLD collective here. Missing features and confusing page layout of the website could affect the using behavior. Most of the patients demanded regular nutritional advices. Some of the participants stated, that they neglected their common eating habits, due to diverse changes during the intervention period (e.g. marriage, job loss, change of shift). Therefore, minor changes in weight status could be explained. Another limitation might be the length of the intervention period. Eight weeks were probably too short to show further improvements in weight status or cardiorespiratory fitness.

What we know is, that...

... NAFLD patients are less active.
... patients have problems to start and maintain an active lifestyle.
... weight loss is not common in exercise interventions.
... nevertheless, exercise has many benefits on liver function.

What this study adds, is, that...

... patients increased their activity level during the tailored intervention period.
... the Web-based support concept is feasible and save for the patients.
... the Web-based support significantly improved the cardio respiratory fitness and body composition.
... the Web-based support achieves similar effects like face to face studies.

Conclusion

In conclusion, the present findings indicate that 8 weeks of Web-based, highly individualized supervised training is save and feasible for patients with NAFLD. In addition, the program improved significantly VO\textsubscript{2peak} and the body composition. In order to influence the risk factor sedentariness sustainably and to enable a long-term lifestyle change, an exercise program is needed which can be...
integrated into everyday life. The Web-based communication as connection between patient and
caregiver might be a useful and cost effective monitoring tool. Close contact to the supervisor can
immediately reduce sport-related doubts and anxieties as well as motivational barriers. The Web-
based design is the first step into a new way of delivering service to a group of patients with NAFLD
and potentially other diseases. Future studies are needed to find out, whether regular interaction
between the patient and the study team can be maintained in long-term. Additionally, the
intervention program, presented here, could be further supplemented with individualized, nutritional
advices provided by a dietician to further improve the weight status. Finally, an expert should rework
the page design and integrate missing features for a more pleasant handling of the page.

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Authors' Contributions
PS, JMS, YH, and DP developed the individual study concepts. DP designed the website. PS and DP
designed the exercise components, and YH and JMS revised the manuscript. All authors read and
approved the final document.

Conflicts of Interest
None declared.

Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AASLD</td>
<td>American Association for the Study of Liver Diseases</td>
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<td>BIA</td>
<td>Bio-Impedance Analysis</td>
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<td>BMI</td>
<td>body mass index</td>
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<td>CRF</td>
<td>cardiorespiratory fitness</td>
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<td>COPD</td>
<td>chronic obstructive pulmonary disease</td>
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<tr>
<td>ECG</td>
<td>electrocardiogram</td>
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<td>FEV1</td>
<td>forced expiratory volume</td>
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<td>FVC</td>
<td>forced vital capacity</td>
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<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<td>HOMA-IR</td>
<td>homeostasis model assessment index</td>
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<td>HR</td>
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<td>HRQOL</td>
<td>health related quality of life</td>
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<td>IAT</td>
<td>individual anaerobic threshold</td>
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<td>LT</td>
<td>lactate threshold</td>
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<td>NAFLD</td>
<td>non-alcoholic fatty liver disease</td>
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<td>NASH</td>
<td>non-alcoholic steatohepatitis</td>
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<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
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<td>WHO</td>
<td>world health organization</td>
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Multimedia Appendix 1
Video clip of the Web-based exercise support concept.
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