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Long-term endurance exercise improves aerobic capacity in patients with relapsing–remitting Multiple Sclerosis: Impact of baseline fatigue

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ABSTRACT

Little is known about the sustainability of exercise effects in patients with relapsing–remitting Multiple Sclerosis (RRMS). We present the results of a prospective, observer-blinded, single-center case control study using a "pre–post" design including 89 ambulatory patients with RRMS and an EDSS score of ≤3.5 who participated in an individualized 12 month aerobic endurance exercise program.
Peak oxygen consumption (VO_2 peak) increased and fatigue levels decreased significantly over time ($p = 0.03$, $p < 0.02$). Subgroup analysis of patients with fatigue (FSS > 4) revealed that the increase of VO_2 peak remained significant after 12 months whereas patients without fatigue did not improve any further after six months. A significant decrease of the FSS score was only observed after nine months ($p < 0.03$) In conclusion, aerobic exercise leads to a sustainable improvement of VO_2 peak over an extended exercise period of 12 months. There is a weak, but significant effect on fatigue levels which becomes detectable only after nine months. Since subgroup analysis revealed that MS patients behaved differently according to their baseline fatigue levels, adjustment to the individual fatigue levels is recommended for future exercise interventions in RRMS patients.

1. Introduction

Physical activity has emerged as an important symptomatic treatment option for patients with Multiple Sclerosis (MS) and has finally superseded the traditional concept that physical exercise might trigger relapses and worsen the natural course of disease [1,2]. In recent years, evidence has accumulated that physical exercise may improve fatigue and peak oxygen consumption (VO_2 peak), various aspects of quality of life (QoL), depression and walking distance [3–7]. Based on these findings detailed recommendations for physical exercise in MS patients have been published [8] and recently been up-dated [9]. However, a direct comparison of the observed effects remains difficult since different types of interventions (e.g. endurance versus resistance training) were applied and MS patients with various degrees of disability and at different stages of the disease were included in the studies [3–5,10–15]. Furthermore, in most studies exercise protocols were only applied for a maximum of three months [3–8]. Therefore, it remains to be demonstrated if the reported beneficial effects are sustainable. Last but not least, it is not known if the impact of baseline fatigue may affect exercise effects in MS patients [3–8,11–16].

The present study was performed to assess the long-term effects of an individualized aerobic endurance exercise in a cohort of ambulatory patients with relapsing–remitting MS and an EDSS ≤ 3.5 over a period of twelve months using a "pre–post" design. The primary endpoints were the change in VO_2 peak and fatigue levels according to the Fatigue Severity Scale (FSS) [17]. As a secondary endpoint, changes in VO_2 peak and fatigue were analyzed according to baseline fatigue.

2. Methods

2.1. Ethics

The study was approved by the Ethics Committee of Deutsche Sporthochschule Köln, Germany. All subjects gave written consent prior to participation.

2.2. Subjects

Participants were recruited from the MS outpatient center "Neurologische Gemeinschaftspraxis Bonn" meeting the following inclusion criteria: (1) A confirmed diagnosis of relapsing–remitting MS (RR-MS) according to the recently revised McDonald's criteria [18]; (2) EDSS of ≤3.5; and (3) age between 18 and 55 years. Patients with secondary or primary progressive MS, a temperature sensitive form of

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MS and a previous history of heart or pulmonary disease as well as arterial hypertension were excluded.

2.3. Neurological examination

A neurological examination was performed to determine the EDSS at baseline and every three months (t1 = baseline; t2 = three months; t3 = six months; t4 = nine months; t5 = twelve months).

2.4. Fatigue Severity Scale (FSS)

The Fatigue Severity Scale (FSS) was used to assess the severity of fatigue [17]. The FSS is the most commonly used questionnaire to quantify fatigue levels in chronic diseases including MS [19]. Validity and reliability have been confirmed in numerous studies [17,20,21]. The FSS is also appropriate to detect changes in fatigue over time [21]. The cut-off value (≥4.0) for the subgroup analysis (fatigue versus non-fatigue) was defined by the baseline value [17]. The FSS questionnaire was completed every three months (t1 = baseline; t2 = three months; t3 = six months; t4 = nine months; t5 = 12 months).

2.5. Measurements of VO_2, heart rate and body fat

All examiners supervising the exercise test were blinded with regard to the EDSS, FSS-scores and the previous test results.

The test protocol used was a modified version of the Naughton protocol [22,23] originally designed for patients with cardiovascular disease and was performed on a treadmill with rubberized slat running surface ("Pro XL" by Woodway GmbH, Germany). The exercise test was discontinued at a respiratory exchange ratio (RER) exceeding 1.1. Further termination criteria were defined as any mention of unease or worsening of pre-existing neurological symptoms, respiratory distress, lack of an adequate elevation or disproportionate elevation of heart rate beyond the known maximum heart rate and muscle pain.

VO_2 was measured by breath-by-breath analysis using the open-circuit spirometry system ZAN 600 USB (nSpire Health GmbH, Germany); O_2 consumption and CO_2 expiration were measured continuously. The recorded VO_2 data were smoothed in the subsequent post-processing with a moving average over three data points. The highest resulting value was defined as VO_2 peak expressed as ml O_2/min/kg with regard to the body weight.

The heart rate (HR) was measured continuously using a chest-strap transmitter allowing digital heart rate monitoring (Polar Electro GmbH, Germany). The highest heart rate recorded during the treadmill exercise test was defined as HR_{peak}.

Body fat was measured by the ten point skin fold method with a Harpenden Skinfold Caliper (Baty international, United Kingdom). Body weight was measured using a digital scale (Seca 910, Seca GmbH & Co. KG, Germany).

Measurements of VO_2, heart rate and body fat were performed at baseline and every three months thereafter (t1 = baseline; t2 = three months; t3 = six months; t4 = nine months; t5 = 12 months).

2.6. Exercise program

According to the baseline evaluation, exercise programs were designed and tailored to the individual physical abilities of each patient. The standard exercise schedule comprised three training sessions per week of 30 minute duration each including two different training methods: One representing an endurance exercise at 65–70% of the individual HR_{peak} ("endurance training") and the other representing an endurance exercise with three superimposed exercise intervals at 70–80% of the individual HR_{peak} of five minute duration each ("interval training"). The weekly exercise schedule included two interval trainings and one endurance training. The training program was based on the recommendations of the American College of Sports Medicine (ACSM) [24].

To monitor the training sessions according to the pre-calculated heart rate ranges, all participants were provided with a chest-strap transmitter allowing digital heart rate monitoring (Polar Electro GmbH, Büttelborn, Germany). Furthermore, individual training self-monitoring was assured by having all participants keeping training diaries which were collected along with the digital heart rate recordings every three months. The training schedules were individually adjusted according to the results of the exercise test.

After twelve months the complete training diary of each participant was collected to analyze the adherence to the training schedules. Upon completion of the study, all participants were offered to receive the final data set of their individual test performances and exercise recommendations along with the provided training equipment.

Early drop-outs between baseline and month three were encouraged to perform a final treadmill test after 12 months.

2.7. Statistical analysis

The determination of the sample size was based on an effect size calculation of the primary outcome parameter "fatigue" as quantified by the FSS-score. Patient recruitment was completed after the required sample size for the prospectively planned subgroup analysis of fatigue versus non-fatigue patients was achieved. Assumption for sample size calculation were $f = .25$, $1\text{-}\beta = .08$ and $\alpha = .05$. The calculation gave a required number of subjects of at least 34, including a supposed drop-out rate of 30%.

The data were explored by a per-protocol analysis. The premises for this were: participation of the subjects in all five test dates and a fully documented training diary.

All analyses of the primary and secondary outcomes were conducted using STATISTICA©10 (StatSoft Europe GmbH, Germany). ANOVA for repeated measurements was applied to examine the longitudinal changes in the whole patient group. For the subgroup analysis (fatigue versus non-fatigue) we used a mixed-model ANOVA with repeated measurements (fatigue: FSS ≥ 4.0; non-fatigue: FSS < 4.0) and changes over time (t1–t5). Significant effects were then confirmed with the Tukey HSD post hoc test ($p < .05$).

A verification of the normal distribution of the outcome variables was performed using the Kolmogorov–Smirnov test. Sphericity of variances was tested using Mauchly's test and in case of violating the sphericity a Greenhouse–Geisser correction was performed by adjustment of the degrees of freedom. The homogeneity of group variances was tested using the Bartlett Test. Effect size is shown as partial eta-square (η_p^2).

3. Results

The study design and the assignment to the two subgroups (fatigue versus non-fatigue) are shown in Fig. 1.

The demographic and clinical characteristics of the total group and the subgroups (fatigue versus non-fatigue) are presented in Table 1.

A total of 92 patients were screened. Three patients were excluded because they did not meet the inclusion criteria. From the 89 patients included in the study, there were 45 drop-outs (51%) over the study period of twelve months. The main reasons for discontinuation were (1) no reason given (n = 14); (2) lack of time (n = 11); (3) inadequate documentation of training activities (n = 10); and (4) physical impairment unrelated to MS (n = 5), pregnancy (n = 4) and relapse (n = 1).

At baseline 18/44 participants (41%) who fully completed the study reported to abstain from any kind of physical exercise and 21/44 (48%) to exercise at random intervals. Only 5/44 subjects (11%) did workout at a gym on a regular basis. None of the patients had ever participated in a specifically designed aerobic endurance training. There was no difference between patients with and without fatigue with regard to their pre-study physical activity.