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European Journal of Sports & Exercise Science is an international, 2017, 5 (1): 1-8

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ISSN:2278-005X

The Effect of a Controlled Exercise Therapy on Physiological Parameters of Energy Metabolism in Patients with Major Depression in the Acute Stage

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ABSTRACT

Objective: *Patients with major depression are affected by a heterogeneous manifestation and severity of the disease, which is also reflected in a reduced motor performance. Under this prospective randomized controlled study, 28 patients (age 49.5 ± 10.8 years; weight 74.2 ± 13.4 kg, height 171.4 ± 12.4 cm, body mass index 25.2 ± 3.5 kg/m^2) were assigned to a control or exercise group. The exercise therapy was four times a week, each sixty minutes in addition to regular treatment during the length of hospital stay. At the beginning and end of the hospital stay, physiological parameters of energy metabolism were collected by means of ergometry. In both groups the BDI showed a significant reduction (t-test, $p<0.05$). Heart Rate$_{max}$, Lactate$_{max}$ and maximum oxygen consumption showed only underlying changes ($p>0.05$). Despite the positive influence on depressive symptoms, the performance of the energy metabolism has only tended to improve in terms of economizing against physical stress. Since the effects are not been final to clarify, further studies are necessary on physiological parameters of energy metabolism in larger patient groups.*

Keywords: Exercise therapy, Major depression, Physiology, endurance, Strength, Vo_{2max}, Lactate, Heart rate

INTRODUCTION

Major depression is one of the most widespread psychological diseases in the last years. Current calculations indicate that the one year prevalence for an EU citizen is 6.9% [1]. According to estimates in 2020, depression will be considered as second most important disease after ischemic heart diseases [2]. The depression comes along with an increased risk of recurrence and chronification as well as increased mortality [3]. According to the Federal Agency of Statistics for Germany a total charge of 5.2 billion euros arise every year. In order to lower the high costs during the rehabilitation process, political health sanctions were resolved. Thereby preventive, health conductive activities were government-funded. Additionally the public gets more sensitized for the disease [3]. Distinctive for the major depression is the diverse and heterogeneous manifestation of symptoms. For example consequences become vivid in the patients' behavior and appearance, the motor function as well as in the motivational and emotional domain. The symptoms have major ramifications on the quality of life and psychosocial wellbeing [4]. Up to 80% of the patients suffer from pain in the musculoskeletal system [5]. Typically, the depressive patients have a decreased level of muscle strength and endurance performance. That elucidates the cohesion of major depression and motor performance [6,7]. The physical capacity of afflicted patients is under the norm level [6], whereas women seem to be affected much more. In comparison with healthy individuals the ergometer performance of patients is reduced by 25%, the maximal oxygen uptake by 20% [8]. The heart rate variability shows un physiological patterns during physical stress [9]. After that, sympathovagal dysfunction and respiratory insufficiency was noted. Possible causes may be medication intake or hormonal factors [10].

Sportive activities can make a great distribution in order to be beneficial for physical and psychological aspects. In the long term, moderate endurance training can increase the relative aerobic capacity (W/kg) and the relative maximal oxygen uptake (ml/min/kg) about 18 resp. 10% [11]. Numerous studies shows the positive effect and therapeutic benefit of physical activities on psychopathological parameters [6,12-19]. Aerobic endurance training can improve the entire level of performance of patients [14,11]. Neither endurance nor strength orientated training is superior to the other form of training [20,21].

Often less practical treatment designs, like single ergometer exercises were used to determine their effect in terms of performance in patients with major depression. The aim of this study was to analyze the effect of an additional practical exercise treatment in stationary acute phase major depression patients regarding the overall psychopathology and physical performance levels.

MATERIALS AND METHODS

Table 1: Participants.

Group	n	Age	Weight	Height	BMI
		[years]	[kg]	[cm]	[kg/m²]
Total	28 (17 female, 11 male)	49.5 ± 10.8	74.2 ± 13.4	171.4 ± 12.4	25.2 ± 3.5
Exercise	14 (8 female, 6 male)	48.6 ± 7.5	65.6 ± 11.8	173.1 ± 10.3	23.5 ± 3.6
Control	14 (9 female, 5 male)	43.9 ± 13.1	78.1 ± 14.1	158.4 ± 46.0	27.0 ± 7.3

Twenty-eight patients (age 49.5 ± 10.8 years; weight 74.2 ± 13.4 kg; height 171.4 ± 12.4 cm; Body Mass Index 25.2 ± 3.5 kg/m²) with major depression were assigned to an experimental and a control group (Tables 1 & 2).

Table 2: Study inclusion and exclusion criteria; F31: Bipolar affective disorder; F31.3: Bipolar affective disorder, current episode mild or moderate depression; F32: Depressive episode; F32.0: Mild depressive episode; F32.1: Moderate depressive episode; F32.2: Severe depressive episode without psychotic symptoms; F32.3: Severe depressive episode with psychotic symptoms; F33: Recurrent depressive disorder; F33.0: Recurrent depressive disorder, current episode mild; F33.1: Recurrent depressive disorder, current episode moderate; F33.2: Recurrent depressive disorder, current episode severe without psychotic symptoms; F33.3: Recurrent depressive disorder, current episode severe with psychotic symptoms; F31.4-F31.9: Bipolar affective disorder; F20-F29: Schizophrenia, schizotypal and delusional disorders.

Inclusion criteria	Exclusion criteria
F31 (F31.30; F31.31)	F31.4–F31.9
F32 (F32.0; F32.1; F32.2; F32.3)	F20–F29
F33 (F33.0; F33.1; F33.2; F33.3)	neurological diseases
hospitalization	acute metabolic diseases
voluntary participation	acute cardiovascular diseases
sports medical permission	acute musculoskeletal disorders

In addition to the standard therapy, patients of the experimental group obtained an exercise intervention. Standard therapy alone was obtained by the control group during the stationary hospitalization. The study was approved by the local ethics committee (Sch IP 091019).

Exercise group (n=14; 8 female, 6 male: 48.6 ± 7.5 years; 65.6 ± 11.8 kg; 173.1 ± 10.3 cm; 23.5 ± 3.6 kg/m^2) was supervised by an exercise therapist. Five patients of the exercise group showed a recurrent depressive disorder with a current severe episode without psychotic symptoms (F33.2). Two additional patients with this disorder exhibited a moderate episode (F33.1). For six people, a major depressive episode without psychotic symptoms has been detected (F32.2). In one person an adjustment disorder with prolonged depressive reaction was observed (F43.21). Other secondary diagnoses were histrionic personality disorder (F60.4) or disorders due to use of alcohol (F10) sedatives/ hypnotics (F13) and tobacco (F17). Antidepressants and tranquilizers were administered. For the treatment of

somatic diseases antihypertensives, hormones to control the thyroid gland, drugs for the regulation of the cholesterol level and antiepileptics were used. Further antibiotics, proton-pump inhibitors and constipationtraetments and hormone preparations were administered.

Control group (n=14; 9 female, 5 male: 43.9 ± 13.1 years; 78.1 ± 14.1 kg; 158.4 ± 46.0cm; 27.0 ± 7.3 kg/ m^2)underwent standard therapy. Four patients showed a recurrent depressive disorder with a current moderate episode without psychotic symptoms (F33.1). Five additional patients with this disorder exhibited a current episode severe without psychotic symptoms (F33.2). Two other patients also had this disorder with a current severe episode and psychotic symptoms (F33.3). In three other persons, an organic mood affective disorder (F06.3) a moderate depressive episode (F32.1) and a severe depressive episode without psychotic symptoms could be detected (F32.2). Additional suspected diagnoses were found in seven participants. These are dependent (asthenic) personality disorders (F60.7), the tarsal tunnel syndrome (G57.3), an unspecified specific personality disorder (F60), a social phobia (F40.1), an alcoholic fatty liver disease (K70.0) a not clearly defined polyneuropathy, a some unspecified degenerative disease of the basal ganglia (G23.8), and generalized anxiety disorder (F41.1), and problems related to life-management difficulty (Z73).

On entrance day, antidepressants and hypnotics were applied. Furthermore, neuroleptics have been used for medical treatment. To regulate the somatic complaints, antihypertensives, anticonvulsants, medications for insulin and cholesterol regulation and proton-pump inhibitors were used. After case history, a medical doctor informed subjects about the purpose of the study. Assigning to an exercise group and a control group was based on the voluntary participation in exercise therapy for ethical reasons. Participation period of the study depended on the time in the hospital. Immediately after admission an ergometer exercise test, to measure the physical performance (25 watts at beginning, 15 watts increase, stage time two minutes) was performed by each patient. During the exercise, oxygen uptake (Cortex Metamax 3B) and heart rate were measured (Suunto Oy Fa.). Before the test and at the end of each step, capillary blood samples (20 .µl) were carried out on the earlobe for lactate analysis (fig. 1). To determine the level of depression, psychologists performed the Beck Depression Inventory (BDI). This self-assessment tool has become an indispensable valid instrument in the treatment of patients with depression [22-24].

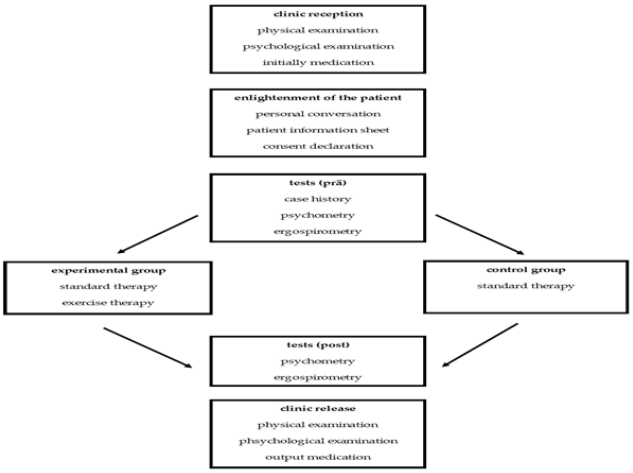

Figure 1: Study design and methodological procedure.

INTERVENTIONS

Standard therapy

Treatments were carried out as a single and/or group intervention. The standard of care in the medical setting included methods for communication, stress management, problem solving, relaxation and nutrition. Furthermore interventions witch promote positive experiences and associations like training of perception and pleasure- and music therapy were in focus. Besides the psychotherapeutic intervention, therapy was made up of ergo therapeutics and physiotherapy and additional activities like animal-assisted therapy.

Exercise therapy

Exercise therapy as intervention additionally to standard therapy took place four times weekly (60 minutes) (Tables 3 & 4). To control the perceived exertion, each participant was familiarized with the modified BORG scale (0-10) before his first exercise therapy [25]. Patients had to feel a load of something strenuous to strenuous (BORG 3-10). In between the parts of the training session and on basis of exercises a determination was made. The main part should be the most intense load (warming BORG 3-5, main part BORG 5-9). The exercise therapy included a training of endurance, strength and flexibility. Endurance and strength was trained twice a week. Each unit was divided into a warm up, main part, and cool down. Warm-up included bicycle ergometer exercise followed by dynamic and static stretching exercises. Running and breathing technique was mediated to participants in the first sessions. The training of basic endurance was performed by walking, running, and nordic walking forms. Strength training consisted of static and dynamic exercise with varying force loads. The main part included strength training of local and global muscle groups. During the therapy, accessories were used to increase the resistance (Thera-bands, medicine balls, small and large exercise balls, tires, mats and dumbbells). Cool down consisted of isometric and dynamic stretching exercises.

Table 3: Exemplary description of the first training session to train the patient's endurance.

Time	Goal	Content	Methods	Organization
7min	Greeting	Settle the organizational course, speedy and easy walking, if applicable: welcoming game,	Continuous method, middle intensity, BORG 4-5, dynamic and static stretching	Patients walk a predefined route,
	Warm Up	stretching		Patients stand in circle form
40min	Acquisition of basic techniques to improve strength and endurance	Speedy walking without concerning about proper technique, therapist explains walking technic (arm movement, step length), patient tries to apply	middle-high intensity, BORG 5-7,	Patients walk a predefined course,
		After 30 min: leg strengthening exercises followed by another 10 min walking	static contraction (30-50% Fmax, 3-5 sets, 15-30s, incomplete rests)	Patients stand in line or circle
10min	Cool down	Stretching	Dynamic and static stretching	patients stand in
		Muscle loosening		circle

Table 4: Exemplary description of the first training session to train the patient's strength.

Time	Goal	Content	Methods	Organization
7 min	Greeting	Bike ergometer,	Continuous method, low intensity at 30 W, 60-70 cycles per min	on bike ergometer,
	Warm Up	stretching		Patients stand in circle form
40 min	Acquisition of basic techniques to improve strength and endurance	Welcoming game (hand medicine ball to each other and say the name),	Playful method, middle intensity, BORG 5-6,	Patients moving around the room,
		Strengthening of big muscle groups without machines (shoulders, chest, back, core, legs, gluteal muscles,	Dynamic and static contraction (30-60% Fmax, incomplete rests), BORG 6-9	Patients lie on roll mats
		Standing: arms, squat		
		On the back: crunch, hip lift		
		On the stomach: entire body stabilization, upper body lift,		
		Stretching after each set		
10min	Cool down	Stretching	Relaxation method, low intensity	
		Relaxation story		Patients lie on roll mats

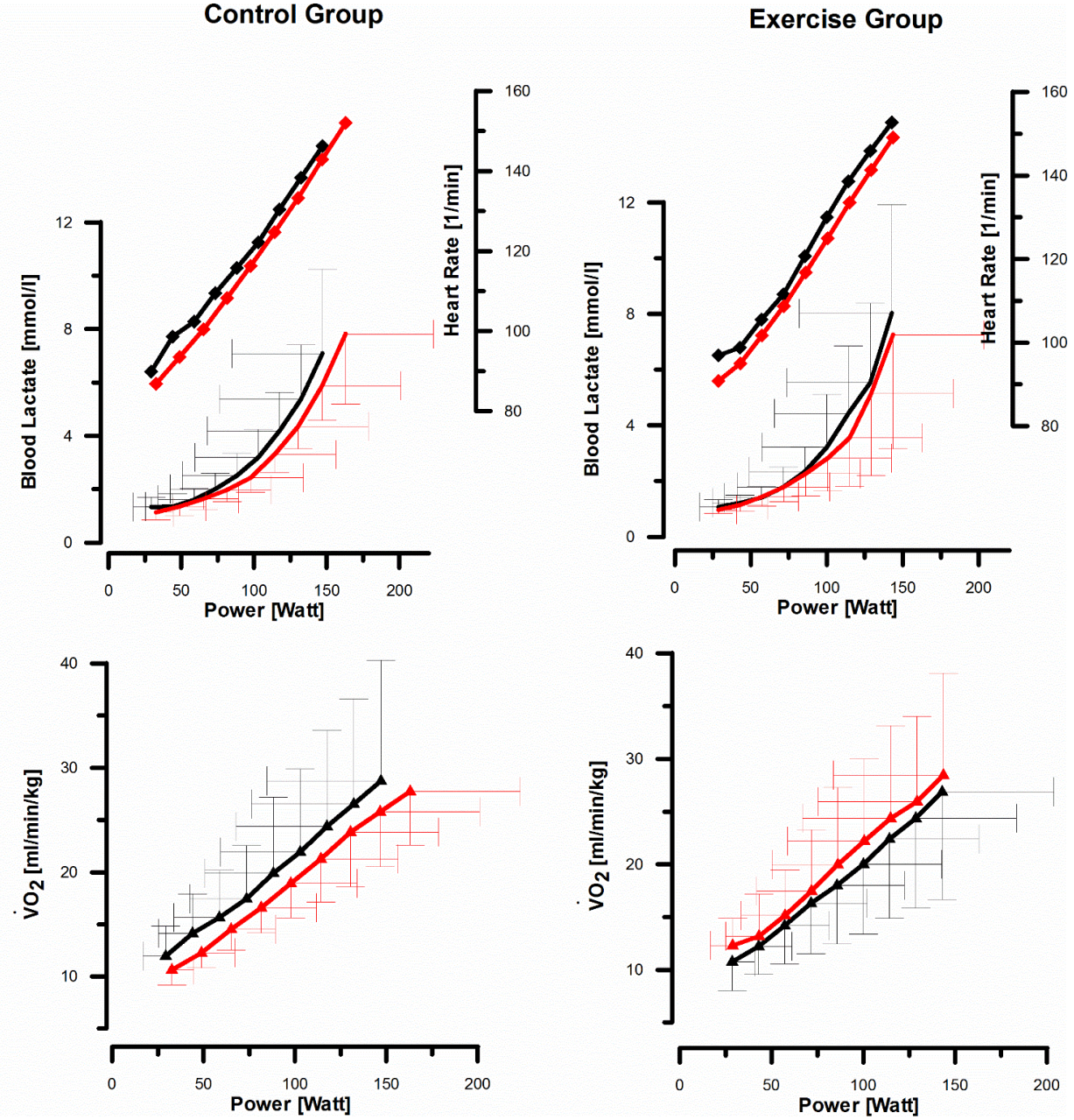

Figure 2: Representation of the mean gradients of physiological variables during stress testing in pre and post comparison of the experimental group and the control group. The black lines mark the pretest. The red lines mark the posttest. The error bars represent the standard deviation.

STATISTICAL ANALYSIS

When evaluating the physiological data, the oxygen intake, power and heart rate at each level of the ergometer exercise test and the fixed 4 mmol/l lactate threshold were considered. Statistical analysis was performed by SPSS 14.0. Mean and standard deviation (SD) were calculated for descriptive statistics. Before assessing significant pre-post differences, within and between groups, the data was tested for normal distribution by Shapiro-Wilk test and homogeneity of variance using Levene's test. This was followed by the analysis using t-test for paired samples. In terms of violation of the conditions, a Wilcoxon test was used. To analyze significant effects between the intervention groups, the analog approach was chosen and tested by ANOVA with repeated measures. In case of violation of the conditions, data analysis was carried out using the Mann-Whitney U test. The significance level was 5%. The magnitude of the treatment effect was calculated by the effect size Cohen´s d [26].

RESULTS

For the analyzing process, the performance of n=21 patients could be included. Within the evaluation of the physiological data, the dataset was reduced. Exercise group subjects (n=13) were 48.9 ± 25.2 days in stationary therapy and participated in 17.4 ± 11.5 intervention training sessions. The control group (n=8) was 64.1 ± 38.1 days in stationary therapy. Regarding the major depression, in both groups a significant decrease of BDI could be recorded. The score within the exercise group was reduced from 26.67 ± 6.37 to 14.17 ± 9.31 points in the post test (T-Test; $p \leq 0.05$). In the pretest the control group recorded a score of 28.38 ± 9.61 which could be improved to 11.38 ± 7.01 in the post test (T-Test; $p \leq 0.05$). In both groups large effects were calculated (Cohen´s d; EG=1.57, CG=1.97). The group which attended the additional exercise therapy managed to reach a maximum performance of 142.85 ± 60.97 Watt in the pretest which could be slightly improved to 144.77 ± 61.03 Watt in the post test (T-Test; p = 0.713). The control group improved on a statistically significant basis from 147 ± 62.34 Watt to 163 ± 60.34 Watt (T-Test; p=0.040). Small effects were defined by Cohens´d of 0.03 (EG) and 0.26 (CG) (Table 5).

The maximal heart rate, maximal lactate and the maximal oxygen uptake each did not show significant differences after ergometry, between pretest and posttest in both groups (Figure 2). Medium effect was only present in the heart rate of the control group (Cohen´s d=0.51), all other effect sizes were only small (Cohen´s d<0.25) (Table3). At a lactate level of 4 mmol/l, the exercise group recorded a non-significant improvement of performance from 119.22 ± 41.86 Watt to 126.43 ± 45.13 Watt (T-Test; p>0.05) whereas the control group improved significantly from pre 126.7 ± 41.3 Watt to post 136.16 ± 46.08 Watt (T-Test; p=0.036). Effect size was small (Cohen´s d; EG=0.16, CG=0.21). Both heart rate and oxygen uptake did not improve significantly. Between both groups no significant difference was found (p>0.05).

Table 5: pre and post values of maximal power, heart rate, blood lactate and oxygen uptake by maximum of subjective stress in loading test from exercise group (EG) and control group (CG) (Mean, SD=standard deviation, Min=minimum, Max=maximum).

Parameter	group	n	Pretest			Posttest			p value pre vs. post	Cohen's d
			Mean ± SD	Min	Max	Mean ± SD	Min	Max	p	d
P_{max} [Watt]	EG	13	142.6 ± 61	55	280	144.8 ± 61	83	280	p>0.05	0.03
	CG	8	147 ± 62.3	45	225	163 ± 60.3	90	240	P ≤ 0.05	0.26
p value between groups			p>0.05			p > 0.05				
$Plac_4$ [mmol/l]	EG	10	119.2 ± 41.9	66.2	196.9	126.4 ± 45.1	65	192.6	p>0.05	0.16
	CG	6	126.7 ± 41.3	83.2	172.2	136.2 ± 46.1	91.8	191.1	p<0.05	0.21
p value between groups			p>0.05			p>0.05				
HR_{max} [1/min]	EG	9	153.8 ± 31.1	96	187	149.3 ± 25.3	108	173	p>0.05	0.16
	CG	7	146.3 ± 21.4	109	170	155.6 ± 14.7	128	176	p>0.05	0.51
p value between groups			p>0.05			p > 0.05				
Lac_{max} [mmol/l]	EG	13	8 ± 3.9	1.7	14.4	7.4 ± 4	1.81	15.7	p>0.05	0.16
	CG	8	7.1 ± 3.2	2.3	11.6	7.8 ± 2.6	4.4	11.6	p>0.05	0.25
p value between groups			p > 0.05			p > 0.05				
VO_2/kg_{max} [ml/min/kg]	EG	13	26.9 ± 10.2	13.3	51.3	28.8 ± 9.8	14.3	47.7	p>0.05	0.19
	CG	8	28.8 ± 11.6	14.7	52.3	27.8 ± 5.2	19.3	33.7	p>0.05	0.11
p value between groups			p>0.05			p>0.05				
BDI [points]	EG	13	26.7 ± 6.4	20	40	14.2 ± 9.3	2	30	p ≤ 0.05	1.57
	CG	8	28.4 ± 9.6	19	43	11.4 ± 7	1	19	p ≤ 0.05	1.97
p value between groups			p>0.05			p>0.05				

DISCUSSION

Aim of the present study was to examine the effect of an additional exercise therapy during acute care hospitalization in patients with major depression on physiological parameters of energy metabolism.

Due to dropouts (n=7), only 21 patients were analyzed. The reasons were premature self-discharge (n=2), discontinuation of the study for personal reasons (n=3) and deterioration of health (n=2). Six patients who dropped out belonged to the control group. When evaluating the heart rate data due to artifacts, five patients could not be included. Analysis of power at 4 mmol/l was waived in five cases, because of not reaching the 4 mmol/l spot.

Reduced exercise capacity of patients with depression shows the necessity of physical training in the therapy [6,27,10]. Compared to the significant improvement in depressive symptoms, only marginal improvements in the performance of the energy metabolism were found in the exercise group. However, these small changes of energy metabolism during exercise could be seen as positive changes in terms of economization of energy metabolism. Only the power at 4 mmol/l blood lactate showed a significant increase in the control group. A significant effect of exercise therapy, performed four times weekly, was not present. Other studies show pronounced changes in performance in patients with depression [14]. Blumenthal compared the effectiveness of a three times weekly endurance-oriented exercise program to patients with moderate to severe depression symptoms over a 16 week period, marked with standard therapy. The study showed that the exercise group and the group with combined therapy achieved a significant improvement in aerobic capacity by oxygen uptake [14]. Further Blumenthal et al. could show, that in respect to the oxygen uptake, a guided or an independently performed exercise program is superior to standard therapy [28]. Worresch et al. also reported similar findings in patients trained at 90% of the individual anaerobic threshold [11]. The only marginal changes in energy metabolism in our current study could be assumed due to low intensity and duration of the training program in comparison with other studies. In addition, patients with severe and acute experience of suffering have been integrated in the study. Due to the metabolic changes in the brain, in severely depressed patients, a physiological adaptation of energy metabolism does not easily occur [29]. Larger effects on aerobic performance have been mostly achieved by means of pure endurance training with an objective load control. Load control, based on objective criteria seems to be questionable in depressed patients because of disturbed stress perception. An earlier investigation showed that objective physical exertion and thus an adequate load control of endurance training to improve aerobic performance in patients with depressive symptoms is often not possible [10]. In addition, there may be a significant limitation of group dynamics using an objective load control by the heterogeneity of performance. Subjective load control in this context, despite anticipated lower effectiveness, turns out to be the tool of choice.

Average duration of intervention was lower compared to other studies. Probably participation of individual patients on exercise workouts was poor. Physiological adaptations by strength-oriented content in the combined training program are to be sought rather in the local muscles, as in cardiorespiratory adaptation phenomena. A measurement of strength should be integrated in future studies with combined training content (strength and endurance).

In principle, endurance and strength training leads to an improvement in depressive symptoms [20,21,30]. The shorter hospital stay in the intervention group compared to the control group should be interpreted with great caution, just as global effectiveness of exercise therapy as an adjunct to standard therapy. It should be noted that in the control group, a higher drop-out rate than in the intervention group was noted.

Limitations are arising due to assignment of patients in the groups. For ethical reasons, the patients were asked about their voluntary participation in the study. Especially the motivation for exercising and the belief in the effectiveness of the intervention may have played a significant role in the decision of the patients to participate. Selection bias therefore could not be excluded [31]. Whether only patients with a certain movement affinity and simultaneously a reduced exercise capacity were included in the experimental group could not be resolved.

In conclusion, we can record that even slight differences of physiological parameters can be interpreted as economization of energy metabolism. The clinical relevance remains unclear, because in both, the exercise and control group, distinct improvements of major depression symptoms were found. Further studies with larger patient samples are necessary, to examine the effect of practical exercise therapy treatments in order of varying severity in major depression, considering the heterogeneity of the patient population.

STATEMENT

The authors state that they have no conflict of interest. No financial support was provided.

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