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Research report

Effects of adjunctive exercise on physiological and psychological parameters in depression: A randomized pilot trial

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ABSTRACT

Objective: Major depressive disorder (MDD) is associated with decreased physical activity and increased rates of the metabolic syndrome (MetS), a risk factor for the development of type 2 diabetes and cardiovascular disorders. Exercise training has been shown to improve cardiorespiratory fitness and metabolic syndrome factors. Therefore, our study aimed at examining whether patients receiving an exercise program as an adjunct to inpatient treatment will benefit in terms of physiological and psychological factors.

Method: Fourty-two inpatients with moderate to severe depression were included. Twenty-two patients were randomized to additional 3x weekly exercise training (EXERCISE) and compared to treatment as usual (TAU). Exercise capacity was assessed as peak oxygen uptake (VO2peak), ventilatory anaerobic threshold (VAT) and workload expressed as Watts (W). Metabolic syndrome was defined according to NCEP ATPIII panel criteria.

Results: After 6 weeks of treatment, cardiorespiratory fitness (VO2peak, VAT, Watt), waist circumference and HDL cholesterol were significantly improved in EXERCISE participants. Treatment response expressed as $\geq$50% MADRS reduction was more frequent in the EXERCISE group.

Conclusions: Adjunctive exercise training in depressed inpatients improves physical fitness, MetS factors, and psychological outcome. Given the association of depression with cardiometabolic disorders, exercise training is recommended as an adjunct to standard antidepressant treatment.

1. Introduction

Unipolar depression is one of the most important causes of lost life years (Whiteford et al., 2013). The comorbidity of MDD with heart disease is common, and the two conditions are considered to have a bidirectional relationship (Whooley and Wong, 2013). Potential factors for an increased cardiovascular morbidity and mortality in patients with depression include increased rates of the metabolic syndrome in depressed patients (Kahl et al., 2012; Vancampfort et al., 2013a, 2013b), changes of body composition with increased intra-abdominal and pericardial fat tissue (Greggersen et al., 2011; Kahl et al., 2014), a dysregulation of the hypothalamus-pituitary-adrenal axis with subsequent hypercortisolism (Stetler and Miller, 2011), and a dysregulation of cytokine function (Dowlati et al., 2010). Furthermore, behavioral factors can be implicated in the relationship between depression and cardiovascular disease. Smoking and depression are consistently associated (Luger et al., 2014). Women with depression display nutritional patterns that are considered less healthy (Jacka et al., 2010). Depression is associated with low objectively assessed physical activity (Vallance et al., 2011), decreased peak oxygen consumption, maximum workload and individual anaerobic threshold (Boettger et al., 2009). Reduced cardiopulmonary fitness is an important predictor of cardiovascular mortality (Dhoble et al., 2014). Low physical activity and cardiovascular fitness predict depressive disorder (Aberg et al., 2012; Mikkelsen et al., 2010). Longitudinal studies suggest that the relationship between physical activity and depression is bidirectional (Azevedo Da Silva et al., 2012; Jerstad et al., 2010).

Meta-analyses show that physical exercise used as a therapeutic intervention may have moderate size effects on depressive symptoms (Cooney et al., 2013). Yet there is little evidence for a long-term effect (Krogh et al., 2011). Only four studies report the results of exercise tests in particular maximum oxygen uptake before and

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after the intervention (Blumenthal et al., 2007; Krogh et al., 2009, 2012; Oeland et al., 2010). Only one study reports on the components of the metabolic syndrome (Krogh et al., 2012).

The aims of the present study were as follows:

1) To assess whether an exercise intervention is feasible with severely depressed patients in an inpatient setting.
2) To assess the effects of an exercise intervention on depressive symptoms.
3) To assess the effects of an exercise intervention on cardiorespiratory fitness and the metabolic syndrome.

2. Materials and methods

The study was approved by the local ethics committee; after complete description of the study to the subjects, written informed consent was obtained. Forty-two consecutive inpatients with MDD treated at the Department of Psychiatry, Social Psychiatry and Psychotherapy, Hannover Medical School were included and randomized either to exercise treatment (EXERCISE; $N=22$) or two treatment as usual (TAU; $N=20$).

Diagnoses was made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria and confirmed with standardized clinical interviews (SCID I/II; German version).

All patients were treated in specialized psychotherapy wards and received cognitive behavioral therapy. Antidepressant treatment was given to 17/22 (77%) patients in the EXERCISE group, and to 15/20 patients (75%) in the TAU group. Details are shown in Table 1.

Medical examination was performed according to the recommendations of the European Heart Association and gave no evidence for previous coronary artery disease, previous myocardial infarction and angioplasty in the group of depressed patients (Perk et al., 2012). None of the patients used ß-blockers or received other cardiologic treatments. Exclusion criteria were acute or chronic infectious disease, acute or lifetime immunological disorders, diabetes mellitus type 1 and type 2, lifetime or current cardiovascular disorders, pregnancy, schizophrenia, mental retardation, bipolar disorder, current substance abuse or dependency, and age younger than 18 years.

Table 1
Anthropometric data and depression scores.

Measure	EXERCISE ($N=22$)		TAU ($N=20$)		
	N	%	*N*	%	*P*
Female	10	45	6	30	n.s.
	Mean	SD	Mean	SD	*P*
Age	44.2	8.5	40.9	11.9	n.s.
Height (m)	1.73	0.08	1.75	0.09	n.s.
Weight (kg)					**0.002**
*t*0	81.2	20.8	82.1	14.9	n.s.
*t*1	80.7	20.2	83.0	15.3	n.s.
BMI					**0.002**
*t*0	26.8	5.1	26.8	4.8	n.s.
*t*1	26.6	5.1	27.1	4.9	n.s.
	N	%	*N*	%	*P*
Antidepressants	17	77	15	75	n.s.
SSRI	5	23	5	25	n.s.
SSNRI	5	23	5	25	n.s.
NDRI	5	23	4	20	n.s.
Agomelatine	6	27	4	20	n.s.
	Mean	SD	Mean	SD	*P*
Smoking (pack-years)	5.5	7.2	5.0	8.5	n.s.
Physical activity before	3.0	1.8	2.6	1.8	n.s.
Drinking	4.1	6.5	0.8	1.6	0.034
BDI-2 sum score					**n.s.**
*t*0	29.4	10.9	28.3	11.2	n.s.
*t*1	13.4*	13.2	15.9*	12.5	n.s.
	N	%	*N*	%	*P*
BDI-2 response	14	64	9	45	n.s.
BDI-2 remission	14	64	8	40	n.s.
	Mean	SD	Mean	SD	*P*
MADRS sum score					**n.s.**
*t*0	23.5	8.7	24.5	10.3	n.s.
*t*1	11.8*	10.4	16.4*	9.4	n.s.
	N	%	*N*	%	*P*
MADRS response	14	64	6	30	0.037
MADRS remission	9	41	5	25	n.s.

Anthropometric and clinical data. Depression scores significantly decreased in both intervention groups (marked with an asterisk). Response expressed as 50% reduction in MADRS sum score was pronounced in the active group. Effects of the intervention were analyzed using multiple measurements ANCOVA and expressed as bold *P* values.

* Means a *P*-value <0.05 concerning within group effects after 6 weeks treatment.

2.1. Behavioral assessment and metabolic syndrome

Depression severity was assessed using the German versions of the 10-item, clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS) and the self-reported, 21-item Beck Depression Inventory-2 (BDI-2). Physical activity was assessed using a 6-point Likert scale with descriptors ranging from "never" [1] to "very often" [5] (Cuppett and Latin, 2002). Smoking habits were measured in pack-years (the number of cigarettes smoked per day × years of smoking/20), and alcohol consumption was measured in drinks consumed per week.

2.2. Blood sampling

Fasting serum samples were collected between 0700 h and 0800 h and stored at −80 °C until the analysis. Concentrations of fasting glucose and lipids were determined with established immunoassays (Roche Diagnostics, Mannheim, Baden-Württemberg, Germany). Factors of the metabolic syndrome (MetS) were determined according to ATP-III criteria (Ford et al., 2002).

2.3. Spiroergometry

For testing parameters of exercise capacity patients performed an incremental exercise test using a spirometric system (Oxycon CPX, CareFusion, Würzburg, Germany) on a speed independent bicycle ergometer (Ergometrics 900s, ergoline, Bitz, Germany) with 60–70 revolutions per minute. The incremental test started with a load of 20 W (W) increasing in 10 W steps every minute and was stopped with the onset of peripheral muscle fatigue and/or dyspnea. The subjective perceived exertion was assessed by the Borg-scale (Borg, 1990). The tests were performed at the beginning and at the end of the hospitalization phase.

Heart rate and oxygen uptake were continuously measured breath by breath while blood pressure and blood lactate concentration were taken at rest, 1 min after the start of testing and every 3 min during the test (Ebio 6666, Eppendorf, Hamburg, Germany); capillary blood samples of 20 µl were taken from the arterialized earlobe, deproteinized and then measured with a Lactate-Analyzer (Ebio, Eppendorf, Berlin, Germany). As marker of oxidative muscle function the anaerobic lactate threshold intensity was determined by the method according to Roecker et al. (intensity corresponding to a blood lactate increase of 1.5 mmol/l above the lowest initial blood lactate concentration (Roecker et al., 2002).

Maximum oxygen uptake (VO_{2max}) is an important criterion for exercise capacity and describes the maximum O_2 the body can utilize per minute under maximum load conditions and is above all dependent on oxygen exchange, transport and utilization systems (Robergs et al., 2010). Hereafter we used the term VO_{2peak} because it is often achieved only by competitive athletes or highly motivated subjects. Another important parameter is the ventilatory anaerobic