Exercise alleviates depression related systemic inflammation in chronic obstructive pulmonary disease patients.

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Abstract

Background: Depression is a highly prevalent co-morbidity in Chronic Obstructive Pulmonary Disease (COPD) which was shown to be associated with a worse course of disease, including reduced quality of life and increased symptoms burden, health-care use, and even mortality. It has been speculated that systemic inflammation may play a role in the presence of depression. Currently, physical activity is an important lifestyle factor that has the potential to modify inflammatory cytokines and depression, however our understanding of how to use exercise effectively in COPD patients to alleviate depression related systemic inflammation is incomplete and has prompted our interest to identify the type and intensities of effective exercise.

Objective: The aim of this study was to measure the changes in depression related systemic inflammation of aerobic exercise training in COPD patients in Jeddah area.

Material and methods: Eighty patients with moderate severity of COPD participated in this study and were divided into two groups; the first group received aerobic exercise, whereas the second group received no exercise training for 12 weeks.

Results: The mean values of tumor necrosis factor-alpha (TNF-α), interleukin-4 (IL-4), interleukin-6 (IL-6), C-reactive protein (CRP) and Beck Depression Inventory (BDI) scores were significantly decreased in in group (A) after treatments, but the changes in group (B) were not significant .Also, there were significant differences between mean levels of the investigated parameters in group (A) and group (B) at the end of the study.

Conclusion: Aerobic exercise is an effective treatment policy to improve depression related to systemic inflammation in patients with chronic obstructive pulmonary disease.

Keywords: Aerobic exercise; depression; inflammatory cytokine; chronic obstructive pulmonary disease.

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Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a highly prevalent chronic lung disease Worldwide. The prevalence is variable between countries, but overall there is a prevalence rate of around 10% in individuals aged 40 and above[1]. In developed countries, COPD is responsible for approximately 4% of all deaths and is the only major condition for which the burden of disease continues to increase, currently being 5th overall in underlying cause of death and 3rd for burden of disease[2,3].

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Chronic Obstructive Pulmonary Disease (COPD) is a medical condition with multiple co-morbidities[4,5]. One of the most common is depression that occurs in 10 to 42% of persons with COPD and is associated with low quality of life[6]. Depression is associated with increased frequency of hospital admissions, prolonged length of stay, increased number of consultations, low compliance with medical treatment and premature death[7,8]. Patients with COPD have a higher prevalence of depression and anxiety than the general population[9,10] and COPD patients have relative risk of 1.69 of developing depression[11].

Patients with depression may not adhere to their management programs such as the pulmonary rehabilitation and smoking cessation. Therefore, depression may lead

to poor clinical outcomes. It has been shown that depression leads to higher health care use with higher admission and relapse rate in emergency department patients. Ultimately, the presence of depression in patients with COPD leads to higher economic burden[12,13].

Chronic obstructive pulmonary disease and depression are significantly associated due to multiple reasons. About 40% of patients with COPD are found to have depression, compared to a prevalence of about 15-20 % in the general population[14]. We found a prevalence of close to 90% of at least mild depression (as measured on the Hamilton depression scale) in patients admitted with COPD[15]. Loss of independence with increasing disability in COPD can cause, or aggravate, depression. A predisposition to depression may increase the risk of smoking, as nicotine has a mood elevating effect. Systemic inflammation may also play a role in depression[16]. Systemic inflammation biomarkers include interleukin-6 (IL-6) and C-reactive protein (CRP) have been shown to be elevated in individuals with depression[17-19] and decreased after antidepressant treatment[20].

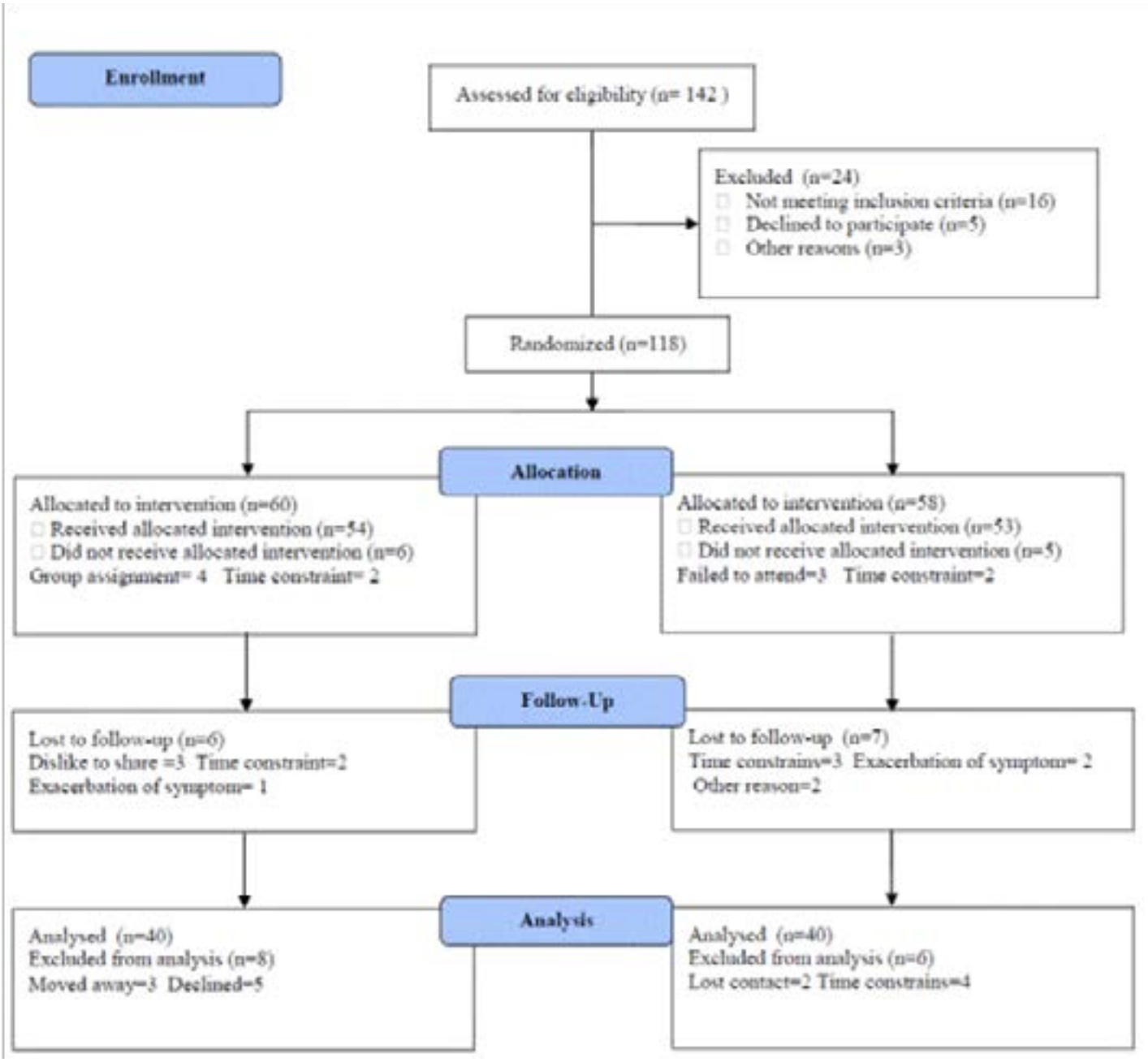
Exercise is a readily available therapeutic option, effective as a first-line treatment in mild to moderate depression[21]. Additionally, exercise has a utility in preventing depression and has beneficial effects on other common co-morbidities (i.e. cardiovascular disease risk factors and glycemic control). A prospective, randomized controlled trial found that exercise was as effective as Sertraline (selective serotonin reuptake inhibitor) for the treatment of depression – the effect size of exercise was 2.0[22]. Several reviews show exercise compares favorably to antidepressants and cognitive behavioral therapy as a first-line treatment for mild to moderate depression[23].

Aerobic exercise training is hypothesized to improve depression related to systemic inflammation but evidence is scarce, so this study aimed to measure depression and systemic inflammation response to aerobic exercises in patients with chronic obstructive pulmonary disease.

Patients and methods

Subjects

Eighty patients with moderate severity of chronic obstructive pulmonary disease according to GOLD[24] were enrolled in this study. Patients with exacerbations in the last 4 weeks were either rescheduled or excluded; their age ranged from 35 to 55 years. Exclusion criteria included ischemic heart disease, congestive heart disease, cerebrovascular disease, dementia, lung cancer, known psychiatric illness, maintenance treatment with systemic corticosteroids (oral, parenteral), active tuberculosis, inflammatory bowel syndrome or insulin dependent diabetes mellitus. Participants were divided into two groups, the first group received aerobic exercises, while the second group was considered as a control group and received no training intervention for three months. The CONSORT diagram outlining the details of the screening, run-in and randomization phases of the study and reasons for participant exclusion can be found in figure (1). Informed consent was obtained from all participants. This study was approved by the Scientific Research Ethical Committee, Faculty of Applied Medical Sciences at King University.



Measurements

1. Inflammatory cytokines measurements: Blood sample was drained from the antecubital vein after a 12-h fasting, the blood samples were centrifuged at + 4 °C (1000 = g for 10 min). Interleukin-6 (IL-6), C-reactive protein (CRP) levels were analyzed by "Immulite 2000". However, tumor necrosis factor-alpha (TNF-α) level was measured by ELISA kits (ELX 50). All analyses were done by Hitachi 7170 Autoanalyser (Tokyo, Japan) and kits (Randox).

2. *Beck depression inventory (BDI):* It measures the depth and behavioral manifestations of depression and consists of 21 items, each of which has four responses of increasing severity. Numerical values from 0–3 were assigned to each statement to indicate the degree of severity. A total score from 0–9 was considered normal, 10–16 reflected mild depression, 17–29 reflected moderate depression and 30 or above was considered severe depression[25].

Procedures

Following the previous evaluation, all patients were divided randomly into the following groups:

1. Patients in Group (A) were submitted to a 40 min aerobic session on a treadmill (the initial, 5-minute warm-up phase performed on the treadmill (Track master 400E, gas fitness system, England) at a low load, each training session lasted for 30 minutes and ended with 5-minute recovery and relaxation phase) either walking or running, based on heart rate, until the target heart rate was reached, according to American College of Sport Medicine guidelines. The program was started with 10 min of stretching and was conducted using the maximal heart rate index (HRmax) estimated by: 220-age. First 2 weeks = 60–70% of HRmax, 3rd to 12th weeks = 70–80% of HRmax.[26]. However, some participants experienced adverse events included attacks of breathlessness (dyspnea), muscle cramp and soreness due to lack of exercise tolerance specially at the beginning of the training program.
2. Patients in Group (B) received no exercise training.

Statistical analysis

Statistical analysis of data was performed using SPSS (Chicago, IL, USA) version 17. The mean values of the investigated parameters obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups. The degree of correlation between BDI scores and cytokine levels was detected by Pearson's product moment correlation coefficients (r). All data were expressed as the mean ± SD. $P<0.05$ indicated statistical significance.

Results

The baseline characteristics of all participants are shown in Table (1). Most participants (65%) were men. Forty participants were assigned to the aerobic exercise group (n = 40; 26 males and 14 females), while the **resistance exercise** group had (n = 40; 27 males and 13 females). None of the baseline characteristics differed significantly between the two groups is listed in table (1).

Table (1): Mean value of demographic data for participants in both groups.

	Mean +SD		Significance
	Group (A)	Group (B)	
Age (year)	33.73 ± 5.14	34.61 ± 4.82	P>0.05
Gender ratio (male/female)	26/14	27/13	P>0.05
Weight (kg)	63.15 ± 6.17	60.98 ± 5.72	P>0.05
Height (cm)	162.32 ± 8.64	160.51 ± 7.68	P>0.05
BMI (kg/m^2)	22.83 ± 3.57	20.88 ± 3.16	P>0.05
FVC (L)	2.51 ± 0.96	2.43 ± 0.85	P>0.05
FEV_1 (L)	1.47 ± 0.63	1.29 ± 0.56	P>0.05
FEV_1/FVC (%)	48.86 ± 9.12	47.53 ± 8.44	P>0.05
MVV (L/minute)	47.16 ± 10.87	45.11 ± 9.58	P>0.05
Total CAT score	19.36 ± 4.15	19.17 ± 4.23	P>0.05
COPDSS	5.97 ± 2.54	6.18 ± 2.46	P>0.05

BMI: Body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in the first second; FEV_1/FVC: Ratio between forced expiratory volume in the first second and forced vital capacity; MVV: Maximum voluntary ventilation; CAT: The COPD Assessment Test; COPDSS: chronic obstructive pulmonary disease severity score.

The mean values of TNF-α, IL-4, IL-6, CRP and Beck Depression Inventory (BDI) scores were significantly decreased in group (A) at the end of the study (table 2), but the changes in group(B)were not significant (table 3).

Table (2): Mean value and significance of TNF-α, IL-4, IL-6,CRP and BDI scores in group (A) before and at the end of the study.

	Mean +SD		T- value	Significance
	Before	After		
TNF- α (pg/ml)	6.46 ± 1.72	4.53 ± 1.28*	7.12	P<0.05
IL-4(pg/ml)	5.71 ± 1.63	3.45 ± 1.52*	6.55	P<0.05
IL-6 (pg/ml)	8.19 ± 2.51	5.27 ± 1.88*	6.84	P<0.05
CRP(mg/dl)	15.34 ± 3.26	9.85 ± 2.44*	7.31	P<0.05
BDI scores	8.26 ± 2.11	5.24 ± 1.97*	6.15	P < 0.05

TNF- α: tumor necrosis factor – alpha; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein ; BDI: Beck Depression Inventory; (*) indicates a significant difference between the two groups, P < 0.05.

Table (3): Mean value and significance of TNF-α, IL-4, IL-6, CRP and BDI scores in group (B) before and at the end of the study.

	Mean +SD		T- value	Significance
	Before	After		
TNF- α (pg/ml)	6.38 ± 1.64	6.51 ± 1.68	0.73	P>0.05
IL-4(pg/ml)	5.62 ± 1.47	5.74 ± 1.51	0.65	P>0.05
IL-6 (pg/ml)	8.23 ± 2.65	8.41 ± 2.62	0.83	P>0.05
CRP(mg/dl)	15.75 ± 3.41	16.08 ± 3.50	0.96	P>0.05
BDI scores	8.43 ± 2.32	8.65 ± 2.49	0.87	P>0.05

TNF- α: tumor necrosis factor – alpha; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP: C-reactive protein; BDI: Beck Depression Inventory.

Also, there were significant differences between mean levels of the investigated parameters in group (A) and group (B) at the end of the study(table 4).

Table (4): Mean value and significance of TNF-α, IL-4, IL-6, CRP and BDI scores in group (A) and group (B) at the end of the study.

	Mean +SD		T- value	Significance
	Group (A)	Group (B)		
TNF- α (pg/ml)	4.53 ± 1.28*	6.51 ± 1.68	6.12	P<0.05
IL-4(pg/ml)	3.45 ± 1.52*	5.74 ± 1.51	5.36	P<0.05
IL-6 (pg/ml)	5.27 ± 1.88*	8.41 ± 2.62	5.27	P<0.05
CRP(mg/dl)	9.85 ± 2.44*	16.08 ± 3.50	6.13	P<0.05
BDI scores	5.24 ± 1.97*	8.65 ± 2.49	5.22	P<0.05

TNF- α: tumor necrosis factor – alpha; IL-4: Interleukin-4; IL-6: Interleukin-6; CRP:C-reactive protein ; BDI: Beck Depression Inventory; (*) indicates a significant difference between the two groups, P < 0.05.

However, table 5 summarizes the relationship between BDI scores and cytokine levels in group (A) at the end of the study. Serum levels TNF-α, IL-4, IL-6 and CRP showed a direct relationship with BDI scores (Table 5). These results confirm that aerobic exercise is appropriate to modulate depression related to systemic inflammation in patients with chronic obstructive pulmonary disease.

Table (5): Correlation coefficient (r) of BDI scores and cytokine levels in group (A) at the end of the study.

	BDI scores
TNF- α (pg/ml)	0.711**
IL-4(pg/ml)	0.643 *
IL-6 (pg/ml)	0.582*
CRP(mg/dl)	0.831**

Spearman's correlation was used *: P < 0.05 **: P < 0.01

Discussion

Globally, chronic obstructive pulmonary disease (COPD) becomes more prevalent and becomes the third cause of death[27,28]. However, by 2030 it is expected to have about 9 million patients to die with COPD every year[29]. Moreover, the economic and health related burden of COPD are enormous[30]. Inflammation is one of key processes in the pathogenesis of COPD[31,32]. The inflammatory cytokines as C-reactive protein (CRP), TNF-α, interleukin-1beta (IL-1β) and IL-6 serve as excellent biomarkers when investigating the potential relationship between inflammation and mood disorders[33,34]. An apparent dose response has been observed with worsening of depressive symptoms correlated with higher levels of inflammatory markers[35]. To date, there are relatively few adequately-powered, trials of an exercise intervention on depression related inflammatory biomarkers in individuals with COPD. In our study, the mean values of TNF-α, IL-4, IL-6, CRP and BDI were significantly decreased after aerobic exercise training. These results are in line with many previous studies.

Dekker et al. stated that a 12-week exercise intervention resulted in a significant decrease in circulating IL-6 in subjects with type 2 diabetes mellitus who underwent an exercise program without weight loss[36]. Also, Mikkelsen et al. proved that life-long endurance exercise was associated with a lower level of the inflammatory markers CRP and IL-6 in elderly subjects[37]. While, Sugawara et al. concluded that the levels of elevated inflammatory

cytokines decreased significantly after intervention with an anti-inflammatory nutrition combined with the low-intensity exercise in stable elderly COPD patients[38]. In addition, there is evidence of lowered IL-6 and TNF-α after prolonged exercise in obese women[39] and decreased TNF-α after 12 weeks of aerobic exercise in patients with heart disease[40]. Moreover, in obese postmenopausal women with type 2 diabetes, 14 weeks of aerobic exercise decreased CRP by 15% and marginally decreased IL-6 ($p=0.07$)[41]. Likewise, 12 week of exercise reduced IL-18 levels by 17.5% in patients with metabolic syndrome[42]. In one of the largest, yet non-randomized, exercise studies conducted to date (HERITAGE Family Study), plasma CRP was significantly reduced with 20 week of aerobic training only in the sub-group of persons with a high baseline CRP[43].

The exact mechanisms by which physical activity may reduce inflammation are not entirely understood, there are some data pointing to factors that may contribute to an effect of repeated bouts of muscle contraction leading to improvements in inflammatory status over time[44]. Exercise training-induced improvements in inflammatory status may also result from the modulation of intracellular signaling path ways and cellular function that are mediated by nitric oxide[45]. Also, exercise training decrease in mononuclear cell production of atherogenic cytokines (TNF-α and IL-1α), while the production of atheroprotective cytokines (IL-10, IL-4, and transforming growth factor beta-1 (TGFβ1)) increased[46]. Exercise training also reduces CD14+CD16+ monocyte number, as well as TNFα production by monocytes[47] and reduces monocyte cell-surface expression of toll-like receptor-4 (TLR4), a lipopolysaccharide (LPS) signaling receptor that likely contributes to attenuation of acute immune responses to infection or trauma[48-50]. Similarly, higher-intensity aerobic exercise training reduces stimulated production of TNF-α by monocytes. Thus, these data point to an adaptive down-regulation of cytokine release from innate immune cells in response to regularly performed muscular contraction[51,52]. Moreover, the potential mechanisms for the anti-inflammatory effect of exercise may include reduced percentage of body fat and macrophage accumulation in adipose tissue, muscle-released interleukin-6 inhibition of tumor necrosis factor-α, and the cholinergic anti-inflammatory pathway[53].

Mota-Pereira and colleagues proved that a home-based exercise program of 30-45 min/day walks, 5 days/week for three moths improved depression and functioning parameters in treatment-resistant 150 patients with major depressive disorder, and contributed to remission of 26% of these patients. Moderate intensity exercise may be a helpful and effective adjuvant therapy for treatment-resistant MDD[54]. Blumenthal et al., had 101 healthy older adults randomized to four months of aerobic exercise, a yoga/flexibility control group, or wait list, assessment of scores from pre- to post-treatment revealed that depressive symptoms were reduced, especially in men[55]. McNeil et al. designed a study to assess the effects of exercise on total level as well as subtypes of depressive symptoms (i.e., somatic, psychological), a community sample of 30 older adults with "moderate" depression was randomized to one of three conditions: supervised exercise, social contact control, or wait list. Participants in the exercise and social contact groups experienced a significant reduction in total and psychological depressive symptoms relative to wait list participants. Only participants in the exercise condition demonstrated significant improvement in somatic symptomatology following treatment[56].

Also, Blumenthal et al. assessed self-reported exercise in a sample of over 2000 men and women (mean age of approximately 60 years) who had suffered a recent myocardial infarction and were either depressed or reported a low level of social support. Patients who reported participation in regular exercise (47% of the sample) had lower depressive symptoms at baseline relative to their sedentary counterparts. In addition, exercisers had lower depression scores six months after they experienced myocardial infarction. Interestingly, exercise participation also was associated with a 50% reduction in mortality over a three-year follow-up period[57]. Meta-analyses from 2010 by Conn included 70 studies with 2679 clinically depressed subjects and suggested that there was a moderate and statistically significant effect size for exercise in treating depression (supervised exercise effect size is 0.372 and un-supervised exercise effect size is 0.522)[58] . Another review conducted for the Cochrane review database, with 27 articles in total and 907 participants, showed evidence suggesting exercise was effective in the treatment of depression (standardized mean difference was _0.82, equaling a large clinical effect)[23].

There are many possible explanations for antidepressant effects of physical exercise and generally they could be divided in two major groups: "psychological" and "biological" mechanisms. Psychological mechanisms involve improvements in self-esteem, self-efficacy[59],self-concept[60], improved coping efficacy[61] and sleep quality[62]. By other hand, some of the main biological mechanisms are reduced production of neuro-inflammatory factors, i.e. TNF-α, IL-6, CRP, IL-1b that affect the main neuroimmune mechanisms potentially leading to symptoms of depression-like behavior[63-67], also release of Beta endorphins[68], the modification in serotonin function proposed by excessive neurotrophins, especially Brain Derived Neurotrophin Factor(BDNF)[69-71].

Strengths and limitations.

The major strength is the supervised nature of the study. Supervising physical activity removes the need to question compliance or to rely on activity questionnaires. Further, all exercise sessions were supervised and adherence to the activities was essentially 100%. Moreover, the study was randomized; hence, we can extrapolate adherence to the general population. On the other hand, the major limitations is only patients with moderate severity of COPD were enrolled in the study, so the value of this study only related to moderate severity of COPD, also small sample size in both groups may limit the possibility of generalization of the findings in the present study in addition a number of confounders as socioeconomic indicators like previous occupation and income which should be controlled as they can affect the outcomes were not measured. Finally, within the limit of this study, aerobic exercise training is recommended for modulation of low grade systemic inflammation and depression among patients with COPD. Further researches are needed to explore the impact of different therapeutic interventions on quality of life and other biochemical parameters among COPD patients.

Conclusion

The current study provides evidence that aerobic exercise is an effective treatment policy to improve depression related to systemic inflammation in patients with chronic obstructive pulmonary disease.

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