Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with Alzheimer's disease.

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Abstract

Background: Alzheimer's disease has a destructive drawbacks on the patient and his/her entire family as this disease badly affects the behavior, cognition and abilities to do activities of daily living (ADL). The physical and mental benefits of exercise are widely known but seldom available to persons suffering from Alzheimer's disease.

Objective: The aim of this study was to measure quality of life, systemic inflammation and psychological well-being response to aerobic exercises in Alzheimer's.

Methods: Forty Alzheimer elderly subjects were enrolled in two groups; the first group received treadmill aerobic exercise, while the second group was considered as a control group and received no training intervention for two months. Assessment of tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), Rosenberg Self-Esteem Scale (RSES),Beck Depression Inventory (BDI), Profile of Mood States(POMS) and SF-36 health quality of life (SF-36 HRQL) were taken before and at the end of the study.

Results: There was a 25.2%, 19.4%, 23.5%, 21.3%, 17.7% , 11.7%, 12.5% and 10.1 % reduction in mean values of TNF-α, IL-6, BDI, POMS, health transition SF-36 subscale, bodily pain SF-36 subscale, role functioning: emotional SF-36 subscale and mental health SF-36 subscale respectively in addition to 15.7%, 13.1%, 12.6%, 11.1%, 13.2% and 11.2 % increase in mean values of RSES, physical functioning SF-36 subscale, role functioning:physical SF-36 subscale, general health SF-36 subscale, Vitality SF-36 subscale and Social functioning SF-36 subscale respectively in group (A) received aerobic exercise training, so that there was a significant reduction in the mean values of TNF-α, IL-6, BDI & POMS and increase in the mean values of SF-36 HRQL subscale scores, RSES in group (A) as a result of aerobic exercise training, while the results of group (B) who received no training intervention 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 ($P<0.05$).

Conclusion: Treadmill walking exercise training is an effective treatment policy to improve quality of life, systemic inflammation and psychological wellbeing in Alzheimer's.

Keywords: Aerobic exercise, quality of life, psychological well-being, systemic inflammation, Alzheimer's.

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Introduction

Alzheimer's disease is a slowly progressive neuropsychiatric disorder affecting mainly the brain regions of cognition and memory[1]. Globally, Alzheimer's disease affects about 27 million people of elderly population, however this number is expected to triple by 2050[2]. Although, aging is the major risk factor in Alzheimer's disease, genetics can be considered have a risk of Alzheimer's disease[3]. The cost of Alzheimer's disease management is high as it is about $183 billion in United State of America, and is expected to be raised by 600% over the next 40 years[4]. Alzheimer's disease not only have a destructive drawbacks on the patient but on his entire family members as this disease badly affects the behavior, cognition and ability to do activities of daily living (ADL)[5].

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Several inflammatory mediators, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) are increased in Alzheimer's patients[6]. Several studies have

established further the presence of inflammatory markers in the Alzheimer's disease brain[7]. CNS inflammation, impaired neuronal insulin signaling, and neuronal dysfunction in Alzheimer's disease may be a consequence of systemic inflammatory processes[8,9]. Neuro-inflammation plays an important role in Alzheimer's disease as well as in depression. Alzheimer's disease is often accompanied by symptoms of depression, anxiety, irritability, and mood instability[10,11]. Ultimately, this could contribute to or accelerate the onset of clinical manifestations of Alzheimer's disease[12].

Psychiatric disturbances affect as many as 90% of patients with Alzheimer's disease and are a major focus of treatment. Depression is one of the most frequent psychiatric complications of Alzheimer's disease, affecting as many as 50% of patients[13-15].

Aerobic exercise training is an effective and cost-efficient alternative therapy for disorders of anxiety and mood disorders[16]. Also, exercise training slows down the progression of cognitive decline[17], improves performance on tests of cognition and psychological well-being[18] and enhances sleep quality[19]. However, the available previous studies involving the impact of exercise training upon the quality of life, psychological wellbeing along with systemic inflammation in Alzheimer's disease is limited in number[20].

Aerobic exercise training is hypothesized to improve cognition, physical performance, functional ability and quality of life. However, the available previous studies involving the impact of exercise training upon the quality of life, psychological well-being along with systemic inflammation in Alzheimer's disease are limited in number; so this study aimed to measure quality of life, systemic inflammation and psychological well-being response to aerobic exercises in Alzheimer's.

Patients and methods

Subjects

Forty elderly patients with Alzheimer's disease with age ranging from 65 to 75 years participated in this study. Exclusion criteria included smokers, subjects with pulmonary, cardiac, renal, hepatic, metabolic and neurological diseases. All the patients who participated in the study were non-smokers and continued on their ordinary diet throughout the study. Following pre-training testing, a randomized block procedure was used to assign qualified participants into two equal groups; group (A) received treadmill aerobic exercise, while the second group (B) was considered as a control group and received no training intervention for two months. The CONSORT diagram outlining the details of the screening, run-in and randomization phases of the study and reasons for participant exclusion 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.

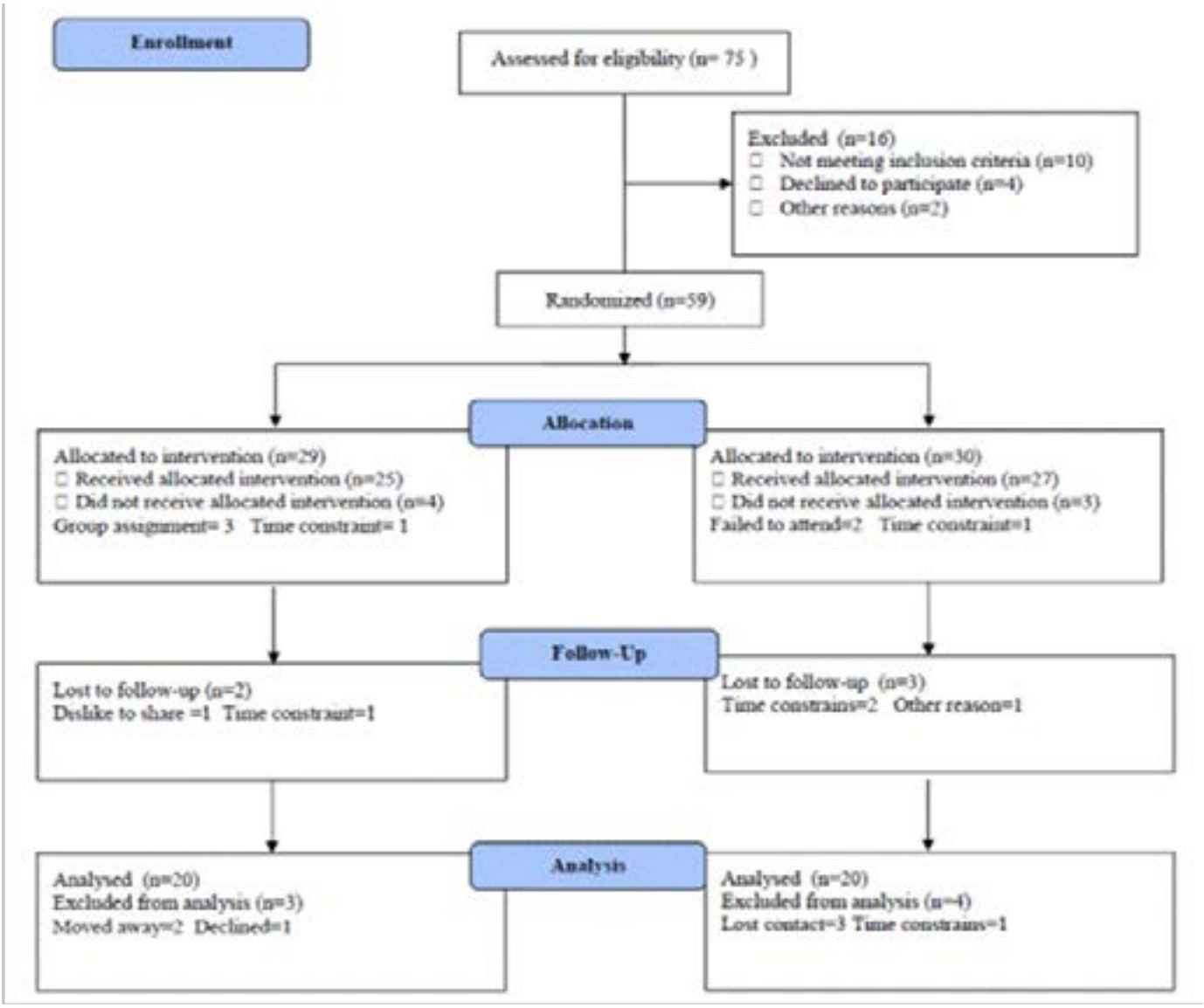

Figure (1) : Subjects screening and recruitment CONSORT diagram.

Measurements

1. Laboratory analysis: Blood samples were 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) level was analyzed by"Immulite 2000" immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, TNF-αlevel was measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA). All analyses were done by Hitachi 7170 Autoanalyser (Tokyo, Japan) and kits (Randox).

2. Psychological well-being: Assessment of psychological well-being included measurement of self-esteem and depression[21]. Self-esteem was evaluated using the Rosenberg Self-Esteem Scale (RSES)[22], which included ten items to be answered on a four point Likert scale. Mood disturbance was measured by Profile of Mood States (POMS)[23]; it assessed the transient emotional state by 65 items on a 5-point Likert scale. This questionnaire evaluated 6 dimensions of mood in order to detect a Total Mood Disturbance score. However, depression was measured using the Beck Depression Inventory (BDI), a twenty-one item was covered to detect the total score for measuring the symptoms of depression[24].

3. Health-related quality of life (SF-36 HRQL): Health-related quality of life was assessed by SF-36 which includes eight subscales: vitality, bodily pain, general health, physical functioning, social functioning, physical Role Functioning, emotional role functioning, and mental health. The SF-36 was a questionnaire for detecting the amount of change in their general health over the past year[25].

Measurements of TNF-α, IL-6, RSES, BDI, POMS and SF-36 HRQL were done before the study (pre-test) and after the study (post-test).

Procedures

Following the previous evaluation, all participants were divided to the following groups:

1. Group (A) participated in treadmill aerobic exercise (Enraf Nonium, Model display panel Standard, NR 1475.801, Holand) which was conducted according to recommendation of aerobic exercise application for elderly approved by the American College of Sports Medicine and the National Institute on Aging[26-27]. Training program included 5 minutes for warming–up in the form of range motion and stretching exercises, 10-30 minutes of aerobic exercise training (60-70% of maximum heart rate) and 10 minutes of cooling down (on treadmill with low speed and without inclination). Participants had 3 sessions/week for 2 months with close supervision by physical therapist.

2. Group (B) received no exercise training.

Statistical analysis

The mean values of the investigated parameters obtained before and after two months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups ($P<0.05$).

Results

Table (1) shows the baseline characteristics of the participants who entered the trial. However, there was a 25.2%, 19.4%, 23.5%, 21.3%, 17.7%, 11.7%, 12.5% and 10.1% reduction in mean values of TNF-α, IL-6, BDI, POMS, health transition SF-36 subscale, bodily pain SF-36 subscale, role functioning: emotional SF-36 subscale and mental health SF-36 subscale respectively in addition to 15.7%, 13.1%, 12.6%, 11.1%, 13.2% and 11.2% increase in mean values of RSES, physical functioning SF-36 subscale, role functioning: physical SF-36 subscale, general health SF-36 subscale, vitality SF-36 subscale and social functioning SF-36 subscale respectively in group (A) who received aerobic exercise training. There was a significant reduction in the mean values of TNF-α, IL-6, BDI & POMS and increase in the mean values of SF-36 HRQLsubscale scores, RSES in group (A) as a result of aerobic exercise training(table 2), while the results of group (B) who received no training intervention were not significant(table 3). 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) ($P<0.05$).

Table (1): Baseline characteristics of study participants.

Characteristic	Group (A)	Group (B)	Significance
Age (years)	68.94 ± 5.76	69.13± 6.12	P>0.05
Gender (male/female)	14/6	15/5	P>0.05
Weight (kg)	67.72 ± 4.91	65.41 ± 5.17	P>0.05
Height (m)	1.65 ± 0.14	1.63 ± 0.12	P>0.05
BMI (kg/m^2)	23.57 ± 3.65	24.13 ± 3.83	P>0.05
SBP (mmHg)	138.65±12.11	140.43 ± 11.82	P>0.05
DBP (mmHg)	83.23 ± 9.42	84.18 ± 9.17	P>0.05

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure

Table (2): Mean value and significance of TNF-α, IL-6, RSES, BDI, POMS and SF-36 subscale scores in group (A) before and at the end of the study.

	Mean ±SD		Significance
	Before	After	
TNF-α (pg/ml)	4.87 ± 1.65	3.64 ± 1.32*	P<0.05
IL-6 (pg/ml)	2.63± 0.84	2.12 ± 0.75*	P<0.05
RSES	22.16 ± 5.61	25.65 ± 6.24*	P < 0.05
BDI	8.01 ± 2.72	6.13 ± 2.91*	P < 0.05
POMS	24.42 ± 4.88	19.21 ± 4.37*	P < 0.05
SF-36 subscale variables			
SF-36: Health transition	2.93 ± 0.71	2.41 ± 0.64*	P<0.05
SF-36: Physical functioning	71.528.64	80.847.25*	P<0.05
SF-36: Role functioning: Physical	81.839.15	92.169.82*	P<0.05
SF-36: Bodily pain	75.167.13	66.326.55*	P<0.05
SF-36: General health	71.438.45	79.359.11*	P<0.05
SF-36: Vitality	54.976.14	62.217.82*	P<0.05
SF-36: Social functioning	86.12 ± 9.31	95.83 ± 10.04*	P<0.05
SF-36: Role functioning: Emotional	92.18 ± 10.18	80.62 ± 8.97*	P<0.05
SF-36: Mental health	84.75 ± 8.66	76.15±7.52*	P<0.05

TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States; (*) indicates a significant difference between the two groups, P < 0.05.

Table (3): Mean value and significance of TNF-α, IL-6, RSES, BDI, POMS and SF-36 subscale scores in group (B) before and at the end of the study.

	Mean ±SD		Significance
	Before	After	
TNF-α (pg/ml)	4.62± 1.48	4.77± 1.51	P>0.05
IL-6 (pg/ml)	2.54 ± 0.96	2.78 ± 1.07	P>0.05
RSES	22.41 ± 5.22	22.25± 5.18	P > 0.05
BDI	7.82 ± 2.43	7.96 ± 2.61	P > 0.05
POMS	23.95 ± 4.56	24.28± 4.73	P > 0.05
SF-36 subscale variables			
SF-36: Health transition	2.71 ± 0.65	2.94 ± 0.67	P>0.05
SF-36: Physical functioning	72.167.98	71.787.65	P>0.05
SF-36: Role functioning: Physical	80.949.53	80.659.23	P>0.05
SF-36: Bodily pain	74.136.54	74.786.38	P>0.05
SF-36: General health	72.218.02	71.957.87	P>0.05
SF-36: Vitality	55.366.11	55.285.94	P>0.05
SF-36: Social functioning	87.28 ± 7.93	87.13 ± 7.90	P>0.05
SF-36: Role functioning: Emotional	90.54± 10.04	91.12 ± 9.86	P>0.05
SF-36: Mental health	83.83+ 9.36	84.17+ 9.51	P>0.05

TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States.

Table (4): Mean value and significance of TNF-α, IL-6, RSES, BDI, POMS and SF-36 subscale scores in group (A) and group (B) at the end of the study.

	Mean ±SD		Significance
	Group(A)	Group (B)	
TNF-α (pg/ml)	3.64 ± 1.32*	4.77± 1.51	P>0.05
IL-6 (pg/ml)	2.12 ± 0.75*	2.78 ± 1.07	P>0.05
RSES	25.65 ± 6.24*	22.25± 5.18	P > 0.05
BDI	6.13 ± 2.91*	7.96 ± 2.61	P > 0.05
POMS	19.21 ± 4.37*	24.28± 4.73	P > 0.05
SF-36 subscale variables			
SF-36: Health transition	2.41 ± 0.64*	2.94 ± 0.67	P>0.05
SF-36: Physical functioning	80.847.25*	71.787.65	P>0.05
SF-36: Role functioning: Physical	92.169.82*	80.659.23	P>0.05
SF-36: Bodily pain	66.326.55*	74.786.38	P>0.05
SF-36: General health	79.359.11*	71.957.87	P>0.05
SF-36: Vitality	62.217.82*	55.285.94	P>0.05
SF-36: Social functioning	95.83 ± 10.04*	87.13 ± 7.90	P>0.05
SF-36: Role functioning: Emotional	80.62 ± 8.97*	91.12 ± 9.86	P>0.05
SF-36: Mental health	76.15±7.52*	84.17+ 9.51	P>0.05

TNF-α: tumor necrosis factor-alpha; IL-6: interleukin-6; RSES: Rosenberg Self-Esteem Scale; BDI: Beck Depression Inventory; POMS: Profile of Mood States, (*) indicates a significant difference between the two groups, P < 0.05.

Discussion

Despite the growing evidence on the benefits of exercise on the health and functioning of older adults with cognitive disorders, the available literature lacks clinical evidence that supports recommendations for exercise guidelines in people with Alzheimer's disease[28]. So, the aim of this study was to detect changes inquality of life, systemic inflammation and psychological wellbeing in response to aerobic exercise training inAlzheimer's. The results of the present study indicated that there was a significant reduction in mean values of Beck Depression Inventory (BDI) and Profile of Mood States(POMS) in response to aerobic exercise training in Alzheimer's. There is a growing body of evidence indicates that aerobic exercise is an effective and cost-efficient treatment alternative for a variety of anxiety and mood disorders, including panic disorder[29]. Craft found that a depressed group who undertook aerobic exercise for nine weeks had significantly higher coping efficacy than a non-exercise control[30]. In a sample of 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[31]. Also, Blumenthal in his study on 156 community dwellers diagnosed with major depression who were randomized to supervised exercise, medication, or a combination of exercise and medication. The 16-week exercise treatment consisted of three weekly sessions of aerobic activity. By the end of the treatment period, each of the three treatment groups experienced a significant reduction in their levels of depression. The treatments did not differ significantly from one another in efficacy. These results suggest that exercise may be a viable alternative to medication in the treatment of depression in older adults[32]. However, Mota-Pereira et al. conducted a study a 12 week, home-based exercise program of 30-45 min/day walks, 5 days/week on 150 individuals with treatment-resistant major depression, results showed improved depression and functioning parameters and contributed to remission of 26% of these patients. Moderate

intensity exercise may be a helpful and effective adjuvant therapy for treatment-resistant major depression[33].

A number of potential mechanisms may be responsible for the reductions in depression associated with physical exercise e.g. physiological mechanisms hypothesized include the central monoamine theory (i.e., exercise corrects dysregulation of the central monoamines believed to lead to depression), as well as consideration of the role of the hypothalamic–pituitary–adrenal (HPA) axis (i.e., some depressed individuals exhibit HPA hyperactivity in response to stress and exercise may regulate this activity)[34,35].

Our results revealed that serum IL-6 and TNF-α were significantly decreased in response to aerobic exercise training in Alzheimer's. Our findings were consistent with Goldhammer et al. who found large (48%; 7.5 to 3.9 mg/L) reductions in serum CRP in 28 elderly coronary heart disease patients in response to 12 weeks of aerobic exercise training as offered in typical Phase II cardiac rehabilitation programs[36]. In a study by Kohut et al. sedentary, low fit older adults aged >64 years were randomized to moderate aerobic exercise training (65-80% heart rate reserve, 3 times per week, 30-45min/day) or flexibility control group for 10 months. Exercisers had a significant reduction in serum C reactive protein (CRP), IL-6, interleukin-18 (IL-18) and TNF-α when compared to the flexibility group[37]. Also, Nicklas et al. examined the effects of 12 months of moderate walking training on plasma CRP and IL-6. Four hundred and twenty four sedentary, overweight/obese (BMI >28), community-dwelling elderly (70-89 years) were randomized to treatment. The exercise intervention resulted in a significant 16% reduction in IL-6. CRP was 32% lower after exercise[38]. Moreover, Ogawa et al. found that 12 week of strength training significantly reduced serum CRP despite having no effect on body weight or waist circumference[39].

The potential mechanisms of exercise training-induced reductions in inflammation in Alzheimer's disease patients include loss of adipose tissue which induced reductions in serum markers of inflammation[40,41]. Exercise training also increases vagal tone[42], which according to the cholinergic anti-inflammatory reflex espoused by Tracy, could lead to reductions in systemic inflammation[43]. Acute exercise activates the hypothalamic-pituitary-adrenal axis and sympathetic nervous systems. Cortisol is known to have potent anti-inflammatory effects44 and catecholamine can inhibit pro-inflammatory cytokine production[45].Several studies have demonstrated that exercise training can down regulate toll-like receptor 4, ligation of which activates pro-inflammatory cascades[46,47].

Furthermore, on analyzing the quality of life changes in response aerobic exercise training in Alzheimer's, we found a significant improvement in the mean values of SF-36 subscale scores. Our findings were consistent with several studies have shown that exercise intervention might enhance health-related quality of life and psychological well-being[48-50]. Mahendra conducted a randomized controlled trial for 3 months follow-up, percentage of participants exercising ≥ 60 min per week increased in the exercise group compared with routine care. Exercise improved levels of physical functioning (SF-36 score) and depression compared with people in routine care (whose levels worsened). At 24 months, longitudinal analyses of all follow-up data revealed improvements in exercise group physical functioning (SF-36) and mobility compared with routine care[51]. Also, Schmitz et al. conducted the German National Health Interview and Examination Survey (GHS) on 7,124 persons, 18–79 years of age. Results revealed that higher levels of physical activity were associated with higher health-related quality of life among persons with mental disorders and physically inactive subjects reported poorer quality of life[52]. Bowen et al. proved that 12-month exercise intervention (225 min/week) improved physical functioning and general health scores among sedentary postmenopausal women (vs. controls)[53]. Improved HRQOL was also noted in another 12-month exercise trial (60 min/day, 3 times/week) among middle-aged adults[54]. While, Imayama et al. conducted a study one middle-aged women (n=100) and men(n=102) who were randomly assigned to either exercise (360 min/week of moderate-to-vigorous aerobic exercise) or control and HRQOL (SF-36)were assessed at baseline and 12 months and proved that this level of exercise may increase HRQOL among overweight men[55]. Similarly, a survey of European adults found that being physically active (≥ 24 MET-h/week) is associated with better mental health compared with being less active (≤24 MET-h/week)[56,57]. Moreover, Hoffmann etal. conducted a study of exercise sessions in a group of 3–5 participants for 1 hour, 3 times per week for 16 weeks. The purpose

of the first 4 weeks of exercise is to accustom the participants to exercising (adaptation exercise). During the next 12 weeks, the exercise is designed to achieve an intensity of 70–80% of heart rate reserve. Results proved that moderate intensity aerobic could improve cognition, quality of life, physical health and functional ability in patients with Alzheimer's disease[58].

Although the exact mechanism for the effect of exercises on mental health is still unknown, several physiological and psychological mechanisms have been proposed, including increased feelings of self-efficacy, self-perceptions of control, reduced emotional strain and physiological responses to stress, and beneficial effects on neurotransmitters[59]. Also, physical activity may have a trophic effect on the brain, particularly the hippo-campus. For instance, exercise increases brain-derived neurotrophic factor (BDNF)[60]. Exercise appears to stimulate neurogenesis[61], enhance neuronal survival[62], increase resistance to brain insults[63,64] and increase synaptic plasticity[65]. Exercise promotes brain vascularization[66,67], mobilizes gene expression profiles predicted to benefit brain plasticity[68]. Social contact may be an important mechanism, and subjects who take regular exercise may, as a result, get positive feedback from other people and an increased sense of self-worth[69].

The current study has important 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. Furthermore, 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 Alzheimer's patients were enrolled in the study, so the value of this study is only related to Alzheimer's in this age group, also the 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 such as socioeconomic indicators like education level, 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 poor quality of life among Alzheimer's. Further researches are needed to explore the impact of different therapeutic interventions on quality of life and other biochemical parameters among Alzheimer's.

Conclusion

The current study provides evidence that treadmill walking exercise training is an effective treatment policy to improve quality of life, systemic inflammation and psychological wellbeing in Alzheimer's.

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