Aerobic exercise modulates cytokine profile and sleep quality in elderly

Shehab M Abd El-Kader[1], Osama H Al-Jiffri[2]

1. Department of Physical Therapy, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.
2. Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Jeddah, Saudi Arabia.

Abstract

Background: Sleep disturbance is a major problem for older adults which can be exacerbated by increased inflammation as aging is associated with increased circulating pro-inflammatory and lower anti-inflammatory cytokines. There is a need to develop alternative medicine techniques to help improve sleep quality in the elderly.

Objective: To investigate the effects of aerobic exercise training on the sleep quality and inflammatory cytokines in elderly subjects.

Material and methods: Forty previously sedentary elderly subjects participated in this study, their age ranged from 61- 67 years. All subjects were randomly assigned to supervised aerobic exercise intervention group (group A, n=25) or control group (group B, n=25). Polysomnographic recordings for sleep quality assessment, interleukin- 6 (IL-6), tumor necrosis factor- alpha (TNF-α) and interleukin-10 (IL-10) were measured before and after 6 months at the end of the study.

Results: There was a significant increase in total sleep duration, sleep efficiency and sleep onset latency in group(A) after 6 months of aerobic exercise training, while, wake time after sleep onset and rapid eye movement (REM) latency significantly reduced after 6 months of aerobic training compared with values obtained prior to aerobic exercise training. Also, the mean values of TNF- α and IL-6 decreased significantly and the mean value of IL-10 significantly increased in group (A) after the aerobic exercise training, however the results of the control group were not significant. Moreover, there were significant differences between both groups at the end of the study.

Conclusion: Exercise training can be considered as a non-pharmacological modality for modifying sleep quality and inflammation among elderly.

Keywords: Sleep quality, inflammatory cytokines, aerobic exercise, aging.

DOI: https://dx.doi.org/10.4314/ahs.v19i2.45

Cite as: *Abd El-Kader SM, Al-Jiffri OH. Aerobic exercise modulates cytokine profile and sleep quality in elderly. Afri Health Sci.2019;19(2): 2198-2207. https://dx.doi.org/10.4314/ahs.v19i2.45*

Introduction

Aging sleep disturbance is a common problem reported by 39–75% of older persons[1,2]. Sleep disturbance may result in fatigue, emotional distress, difficulty with concentration and memory, daytime dysfunction and an increased risk of falls; it has a negative impact on morbidity, mortality and quality of life[3,4]. However, sleep disturbance is not an inevitable part of aging[3]. The most frequent changes in sleep caused by aging are increases in the frequency nighttime awakenings and arousals and a decrease in the time spent in deep sleep[5]. Additional changes in sleep can also include increases in stages 1 and 2 sleep time, decreases in stages 3 and 4 sleep time, decreases in rapid eye movement (REM) sleep, increases in sleep fragmentation, decreases in total sleep time, decreases in sleep efficiency and increases in sleep disturbances[5-7].

Because sleep complaints and sleep-related problems increase with age, it is possible that they are promoted by

Corresponding author:
Shehab M Abd El-Kader
Department of Physical Therapy,
Faculty of Applied Medical Sciences,
King Abdulaziz University,
P.O. Box 80324, Jeddah, 21589,Saudi Arabia.
Email: salmuzain@kau.edu.sa

low-grade systemic inflammation present in older individuals[8,9]. Indeed, this age-dependent pro-inflammatory state may be associated with several pathophysiological conditions associated with sleep complaints[10], such as sleep disturbance[11–13], in addition to many other age-related diseases, such as arteriosclerosis, dementia, osteoporosis, cancer[14] and obesity[15]. Taken together, these factors can contribute to a poor quality of life for elderly individuals.

Because sleep complaints and sleep-related problems increase with age, it is possible that they are promoted by low-grade systemic inflammation present in older individuals[16]. Indeed, this age-dependent pro-inflammatory state may be associated with several pathophysiological conditions associated with sleep complaints[17], such as sleep disturbance[18,19]

Sleep disturbance should be recognized and managed with either pharmacological or non-pharmacological treatment. Lower physical activity level was found to be a significant risk factor for insomnia[20]. Previous studies have reported that moderate-intensity exercise, such as Tai Chi or yoga may improve sleep quality[21-23]. In addition, participation in a regular exercise program can also have positive effects on sleep quality[24], mood[25], and cognitive abilities[26]. A meta-analysis of 12 studies indicates that regular exercise increases total sleep time[27]. In addition, epidemiological data based on self-reports consistently support the view that acute and chronic exercise promotes sleep[28].

Most studies examining the effects of exercise on sleep have focused on young good sleepers or fit athletes[28,29]. The limited data available in older adults also indicate an association between physical activity levels and sleep quality[30]. There is also evidence that increasing physical activity level can improve sleep quality in older adults[30,31]. For example, in sedentary older adults, a 16 week program of mild to moderate intense physical activity improved self-rated sleep quality[24]. In another study, exposure to daily physical and social activity for just 2 weeks also had positive effects on sleep quality in older adults[32]. Furthermore, in older adults with depression, progressive weight training significantly improved measures of both subjective sleep quality and depression[25]. Moreover, moderate training may reduce resting plasma concentrations of pro-inflammatory cytokines and increase anti-inflammatory cytokines, consequently improving the quality of sleep[18].

The aim of the study was to investigate the effect of aerobic exercise training on the sleep quality and inflammatory cytokines in elderly subjects.

Patients and methods

Subjects

Fifty healthy community dwelling sedentary men and women who were 61 years or older with symptoms of difficulty falling asleep and/or staying asleep, given the opportunity to sleep, accompanied by impairment in daytime functioning for at least 3 months. In addition, participants were required to be independent in activities of daily living and without significant cognitive deficits and have a sleep efficiency (SE) less than 80% and/or awaken earlier than desired if before 6 AM and a total sleep time of less than 6.5 hours; Also, sedentary, defined as participation in exercise of mild to moderate intensity for less than 30 min per day and less than 2 times per week on a regular basis. Exclusion criteria included history of major psychiatric disorder as mania or alcohol or substance abuse or other neurological disorders, significant depressive symptoms, serious medical conditions or cardiopulmonary disease that contraindicate exercise, current use or use within the past month of psychoactive, hypnotic, stimulant or analgesic medications, shift work or other types of self-imposed irregular sleep schedules, smoking or caffeine consumption greater than 300 mg per day. This study used a randomized parallel pre-post design. Participants were randomly assigned to either an aerobic exercise intervention group (group A) who participated in the exercise intervention conducted 3 times per week for 6 months or non-physical activity intervention and control group(group B) who received no training intervention and asked to follow their usual life style. This study was approved by the Ethical Committee for Scientific Research, Faculty of Applied Medical Sciences, King Abdulaziz University. All participants provided written informed consent.

Measurements and procedures

A. Sleep measures: All participants underwent polysomnographic (PSG) recording before and after the exercise training. For the pre-intervention assessment, PSG recording was performed over 2 nights. The first night served as an adaption night; 48 hour later, the participants returned for another night of PSG recording. The post-training PSG assessment occurred at least 30 hours after the last exercise session. The participants arrived at the sleep laboratory at 21:00; the PSG recording started

and finished according to each volunteer's habitual sleep schedule. The room used for the recordings had a large comfortable bed, acoustic isolation, and controlled temperature and light. Recordings were conducted by a trained sleep technician using a digital system (Philips-Respironics, USA). The following parameters were analyzed: (a) total sleep time (in min), defined as the actual time spent asleep; (b) sleep latency (in min), defined as the time from lights out until the onset of three consecutive epochs of stage 1 or deeper sleep; (c) sleep efficiency, defined as the percentage of total recording time spent asleep; (d) wake after sleep onset (in min), defined as the total time scored as wakefulness between sleep onset and final awakening; (e) sleep stages 1, 2, 3, and 4 as well as REM sleep as percentages of total sleep time; and (f) latency to REM, defined as the time from sleep onset until the first epoch of REM sleep[33].

B. Inflammatory cytokines assessment: Blood samples were collected from the antecubital vein after a 12-hour fasting, the blood samples were centrifuged at + 4 °C (1000 = g for 10 min). Interleukin-6 (IL-6) and Interleukin-10 (IL-10) levels were analyzed by "Immulite 2000"immunassay analyzer (Siemens Healthcare Diagnostics, Deerfield, USA). However, tumor necrosis factor-alpha (TNF-α) was measured by ELISA kits (ELX 50) in addition to ELISA microplate reader (ELX 808; BioTek Instruments, USA).

C. Aerobic exercise training program: 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 at a low load, each training session lasted 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 began with 10 min of stretching and was conducted using the maximal heart rate index (HRmax) estimated by: 220-age. First 2 months = 60–70% of HRmax, second 4 months = 70–80% of HRmax34.

Statistical analysis

The mean values of the investigated parameters obtained before and after six 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

The two groups were considered homogeneous regarding the demographic variables. The mean age of the group (A) was 64. 98 ± 4.15years, and the mean age of group (B) was 65.72 ± 3.86years. There was no significant differences in age, weight, height, body mass index (BMI), waist circumference, hip circumference, systolic blood pressure and diastolic blood pressurebetween both groups (figure 1).

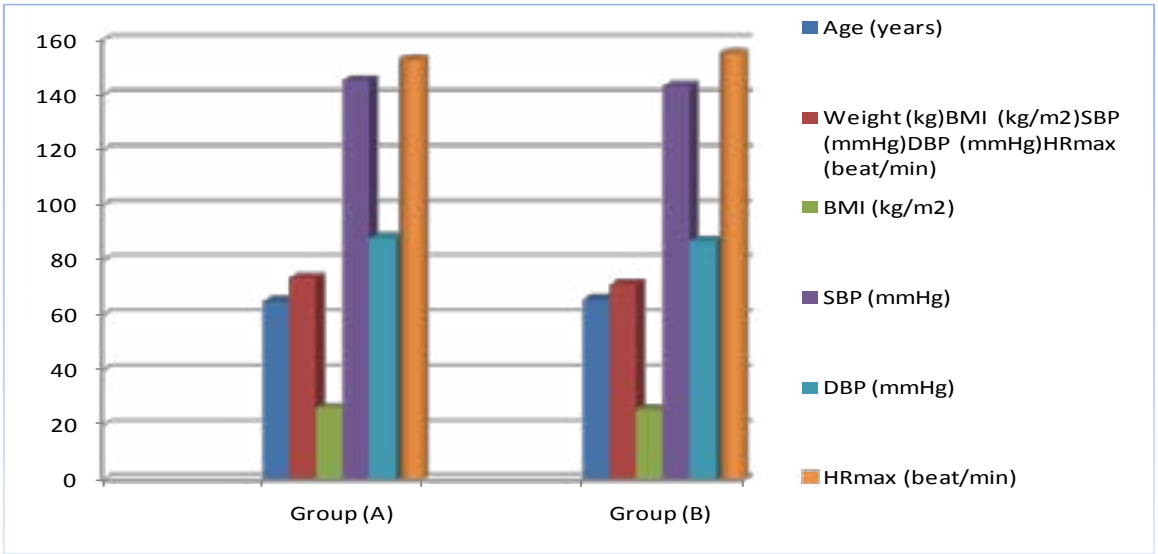

Figure (1): Baseline characteristics of study participants.

Regarding sleep quality parameter, there was a significantincrease in the total sleep duration, Sleep efficiency and Sleep onset latency in group(A) after 6 months of aerobic exercise training, while, awake time after sleep onset and REM latency significantly reduced after 6 months of aerobic training compared with values obtained prior to aerobic exercise training (table 1).

Table 1: Mean value and significance of polysomnographic parameters, TNF-α, IL-6 and IL-10 in group (A) before and after treatment.

	Mean + SD		t- value	Significance
	Before	After		
Total sleep duration (min)	320.27 ± 26.14	336.81 ± 29.25*	8.24	0.006
Sleep efficiency (%)	72.31 ± 10.28	81.24 ± 11.47*	7.13	0.002
Sleep onset latency (min)	12.85 ± 3.16	15.12 ± 3.84*	6.91	0.018
Awake time after sleep onset (min)	77.56 ± 12.49	63.44 ± 10.23*	7.18	0.003
REM sleep latency (min)	80.26 ± 13.41	65.12 ± 11.37*	7.64	0.001
TNF-α (pg/mL)	5.14 ± 1.48	3.25 ± 1.21*	5.83	0.016
IL-6 (pg/mL)	2.73 ± 0.97	1.64 ± 0.75*	4.39	0.019
IL-10 (pg/ml)	6.12 ± 1.25	8.34 ± 1.63*	6.17	0.004

REM: rapid eye movements; TNF-α: tumor necrosis factor – alpha; IL-6: Interleukin-6; IL-10: Interleukin-10; (*) indicates a significant difference between the two groups, $P < 0.05$.

Moreover, the mean values of TNF-α and IL-6 decreased significantly and the mean value of IL-10 significantly increased in group (A) after the aerobic exercise training, however the results of the control group were not significant (table 2). Also, there were significant differences between both groups at the end of the study (table 3).

Table 2: Mean value and significance of polysomnographic parameters, TNF-α, IL-6 and IL-10 in group (B) before and at the end of the study.

	Mean + SD		t- value	Significance
	Before	After		
Total sleep duration (min)	325.19 ± 28.25	318.65 ± 28.72	1.95	0.124
Sleep efficiency (%)	74.23 ± 12.46	71.18 ± 11.95	1.64	0.061
Sleep onset latency (min)	13.92 ± 4.15	12.74 ± 3.88	1.21	0.152
Awake time after sleep onset (min)	75.14 ± 11.52	77.28 ± 11.49	1.38	0.076
REM sleep latency (min)	78.68 ± 12.66	79.56 ± 12.41	1.16	0.087
TNF-α (pg/mL)	4.71 ± 1.53	4.95 ± 1.62	0.87	0.319
IL-6 (pg/mL)	2.57 ± 0.91	2.82 ± 0.93	0.84	0.173
IL-10 (pg/ml)	6.44 ± 1.37	6.27 ± 1.35	0.92	0.265

REM: rapid eye movements; TNF-α: tumor necrosis factor – alpha; IL-6: Interleukin-6; IL-10: Interleukin-10.

Table 3: Mean value and significance of polysomnographic parameters, TNF-α, IL-6 and IL-10 in group (A) and group (B) at the end of the study.

	Mean + SD		t- value	Significance
	Group (A)	Group (B)		
Total sleep duration (min)	336.81 ± 29.25*	318.65 ± 28.72	9.13	0.004
Sleep efficiency (%)	81.24 ± 11.47*	71.18 ± 11.95	7.86	0.006
Sleep onset latency (min)	15.12 ± 3.84*	12.74 ± 3.88	7.65	0.012
Awake time after sleep onset (min)	63.44 ± 10.23*	77.28 ± 11.49	7.92	0.008
REM sleep latency (min)	65.12 ± 11.37*	79.56 ± 12.41	8.17	0.007
TNF-α (pg/mL)	3.25 ± 1.21*	4.95 ± 1.62	6.74	0.021
IL-6 (pg/mL)	1.64 ± 0.75*	2.82 ± 0.93	5.15	0.034
IL-10 (pg/ml)	8.34 ± 1.63*	6.27 ± 1.35	6.81	0.002

REM: rapid eye movements; TNF-α: tumor necrosis factor – alpha; IL-6: Interleukin-6; IL-10: Interleukin-10; (*) indicates a significant difference between the two groups, $P < 0.05$.

Discussion

Aging sleep disorder is an increasingly prevalent serious problem that affects more than 20% and 30%, if older adults in western countries[35]. Lack of sleep can affect an individual's quality of life, social interaction and mood[36]. To date, the most common treatments for sleep disorders remain pharmacological agents as several systematic reviews have reported that hypnotics improve sleep quality[37-39]. However, the increased risk of adverse events was found to be statistically significant and poses potential risks for older individuals for falls or cognitive impairment[39]. Although research has found that pharmacological treatment appears an effective treatment for sleep disorders, evidence of its sustained efficacy is lacking[40]. Moreover, non-pharmacological approaches have a long history of treating sleep disorders, among which physical exercise is increasingly regarded as an effective way[41,42].
Concerning sleep quality parameter, there was a significant increase in the total sleep duration, sleep efficiency and sleep onset latency in group (A) after 6 months of aerobic exercise training, while, awake time after sleep onset and REM latency significantly reduced after 6 months of aerobic training compared with values obtained prior to aerobic exercise training (table 2), these results are in line with many previous studies[43-53].

Reid et al. had Seventeen sedentary elderly subjects with insomnia who had 16 weeks of aerobic physical activity. The clearly stated that physical activity improved sleep quality on the global Pittsburgh Sleep Quality Index (PSQI) score, sleep latency, sleep duration, daytime dysfunction and sleep efficiency[43]. Where, Lira et al. conducted a study on fourteen male sedentary, healthy, elderly volunteers performed moderate training for 60 minutes/day, 3 days/week for 24 week at a work rate equivalent to the ventilatory aerobic threshold. They proved that sleep parameters, awake time and REM sleep latency were decreased after 6 months exercise training in relation baseline values[44]. In addition, Yang and colleagues completed a systematic review with meta-analysis of six randomized trials and provided data on 305 participants (241 female). Each of the studies examined an exercise training program that consisted of either moderate intensity aerobic exercise or high intensity resistance exercise. The duration of most of the training programs was between 10 and 16 weeks. All of the studies used the self-reported Pittsburgh Sleep Quality Index to assess sleepquality. Compared to the control group, the exercise group had significantly reduced sleep latency and medication use[45]. While, Chen and coworkers enrolled twenty-seven participants in 12 weeks of Baduanjin exercise training, they showed that overall sleep quality, subjective sleep quality, sleep latency, sleep duration, sleep efficiency, and daytime dysfunction significantly improved after 12 weeks of intervention[46]. In addition, Santos et al. had twenty-two male, sedentary, healthy, elderly volunteers performed moderate training for 60 min/day, 3 days/week for 24 week at a work rate equivalent to their ventilatory aerobic threshold, their findings suggest that aerobic exercise training increased aerobic capacity parameters, decreased REM latency and decreased time awake[47]. Moreover, Passos and colleagues concluded that a 4-month intervention of moderate aerobic exercise delivered to twenty-one sedentary participants with chronic primary insomnia had polysomnographic data significantly improvements following exercise training, where total sleep time, sleep efficiency and rapid eye movements significantly increased. In addition, sleep onset latency and wake time after sleep onset significantly decreased following exercise training[48]. Regarding the mechanism underlying the effect of exercise on sleep, although the mechanisms by which training can improve sleep quality are not well understood. It has been proposed that exercise training improves sleep quality through increasing energy consumption, endorphin secretion, or body temperature in a manner that facilitates sleep for recuperation of the body[49-51]. Moreover, moderate training may reduce resting plasma concentrations of pro-inflammatory cytokines and increase anti-inflammatory cytokines, consequently improving the quality of sleep[52,53].

Our results demonstrate that aerobic exercise training causes reduction in TNF-α and IL-6 levels, in addition to increase in IL-10 level which suggests that exercise training can reduce inflammation in elderly individuals with more significant changes following aerobic exercise training. Regarding the aerobic exercise training, our results agreed with several studies have shown that aerobic exercise promotes the modulation of inflammation[54-56]. Several large cohort studies have found a relationship between self-reported physical activity levels and systemic markers of inflammation: higher levels of physical activity are coupled to lower levels of circulating inflammatory markers in elderly individuals[57-59]. While, Nicklas et al.

showed that regular aerobic exercise training was efficient in lowering IL-6 levels even without weight loss[60]. However, Kohut et al. reported that 10-months of aerobic exercise significantly reduces serum inflammatory mediators in older adults[61]. In addition, Bote et al. demonstrated that 8-months (2 sessions/week, 60-min/session) of aquatic-based exercise training tempered neutrophil activation (chemotaxis) and decreased systemic levels of IL-8 and noradrenalin compared to controls[62]. In addition, Ploeger et al. who reported that moderate aerobic exercise training has been recommended as an anti-inflammatory therapy[63]. Where, Gatta and co-workers examined the expression of cytokines at both rest and following a bout of isokinetic exercise performed before and after 12 weeks of resistance exercise training in 8 young and 8 elderly. They stated that expression of pro-inflammatory cytokines MCP-1, IL-8 and IL-6 increased substantially after acute exercise. By contrast, the expression of the anti-inflammatory cytokines IL-4, IL-10 and IL-13 increased only slightly (or not at all) after acute exercise. These responses were not significantly different between young and elderly men, either before or after 12 weeks of exercise training. They concluded that, regular exercise training might help to normalize this inflammatory response in the elderly[64]. Moreover, Santos et al. stated the levels of IL-6 and TNF-α and the ratio of TNF-α/IL-10 were decreased, whereas IL-10 levels were increased after 24 weeks moderate aerobic training.[47]

The three possible mechanisms of exercise anti-inflammatory effects include reduction in visceral fat mass65; reduction in the circulating numbers of pro-inflammatory monocytes[66] and an increase in the circulating numbers of regulatory T cells[67]. Moreover, Hong and colleagues show that cardiorespiratory fitness is associated with reduced low grade inflammation that may in part be mediated by enhancing the ability of immune cells to suppress inflammatory responses via adrenergic receptors[68]. The training-induced sleep changes associated with an improvement in the inflammatory profile, demonstrated by a significant decrease in the level of inflammatory cytokines which were sufficient to improve global sleep phases as older individuals may demonstrate elevated inflammatory cytokines concentrations, which can increase non-rapid eye movement (NREM) sleep by impairing a subset of sleep-related neurons in the preoptic area/basal forebrain[18,19,69].

The current study has important strengths and limitations. The major strength is the supervised nature of the study. All exercise sessions were supervised essentially 100%. Moreover, the study was randomized; hence, we can extrapolate adherence to the general population. In the other hand, the major limitations is only elderly enrolled in the study, so the value of this study only related to this age group , also small sample size in both groups may limit the possibility of generalization of the findings in the present study. Finally, within the limit of this study, exercise training is recommended for improving sleep quality and modulation of low grade systemic inflammation among elderly. Further researches is needed to explore the impact of other therapeutic modalities on quality of sleep and other biochemical parameters among elderly.

Conclusion

Exercise training can be considered as a non-pharmacological modality for modifying sleep quality and inflammation among elderly.

Acknowledgment

This project was funded by the Deanship of Scientific Research (DSR), King Abdulaziz University, Jeddah, under grant no. (G-7-142-1439). The authors, therefore, acknowledge with thanks DSR technical and financial support.

Conflict of interest

None declared.

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