



Moderate exercise training modulates cytokine profile and sleep in elderly people

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ABSTRACT

Aging causes several physiological alterations, including alterations in sleep. It is possible that difficulty sleeping can be exacerbated by increased inflammation in older individuals. Moderate exercise training may be a modality of non-pharmacological treatment for sleep disorders and inflammation. We aimed to assess the effects of moderate exercise training on sleep in elderly people as well as their cytokine profiles. Additionally, we examined the effect of exercise training on quality of life parameters using a SF-36 questionnaire. 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. The environment was kept at a temperature of 23 ± 2 °C, with a humidity of $60 \pm 5\%$. Blood and polysomnograph were collected twice: at baseline (1 week before training began) and after 6 months of training. Training increased aerobic capacity parameters ($p < 0.0001$), decreased REM latency ($p < 0.02$), and decreased time awake ($p < 0.05$). After training, the levels of IL-6 ($p < 0.0001$) and TNF- α ($p < 0.0001$) and the ratio of TNF- α /IL-10 ($p < 0.0001$) were decreased, whereas IL-10 levels were increased after training ($p < 0.001$). Furthermore, exercise training was shown to improve quality of life parameters. Our results suggest that 6 months of training can improve sleep in the elderly and is related to the anti-inflammatory effect of moderate training, which modifies cytokine profiles.

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1. Introduction

Aging is characterized by several physiological and functional changes, including a poor homeostatic balance and an increased incidence of pathology, which eventually results in death [1]. In older individuals, these physiological changes impair the function of the immune system, referred to as immunosenescence, and also negatively affect the cardiovascular, respiratory, and nervous systems, which can disrupt sleep [2,3].

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 [4]. 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 (i.e., apnea and insomnia) [2,4,5]. 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 [6,7]. Indeed, this age-dependent pro-inflammatory state may be associated with several pathophysiological conditions associated with sleep complaints [8], such as sleep disturbance [10–12], in addition to many other age-related diseases, such as arteriosclerosis, dementia, osteoporosis, cancer [3] and obesity [9]. Taken together, these factors can contribute to a poor quality of life for elderly individuals.

Acute and chronic exercise may be a modality of non-pharmacological treatment for sleep disorders [12], particularly in older individuals [13]. Acute physical exercise results in a transient reduction in sleepiness depending on the intensity and the time of day at which the exercise is performed. This reduced sleepiness may be directly caused by physical exercise, which increases total sleep time, delays REM sleep, increases stage 4 sleep time and reduces REM sleep time [14–17]. However, the mechanisms by which training can improve sleep quality are not well understood. Moderate training may reduce resting plasma concentrations of pro-inflammatory cytokines and increase anti-inflammatory cytokines, consequently improving the quality of sleep [10].

Our aim was to assess the effect of moderate exercise training on cytokine levels and sleep quality in elderly people. Our hypothesis was that moderate exercise training could improve sleep and

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that this improvement would be modulated by a decrease in inflammation, leading to a better quality of life.

2. Methods

2.1. Subjects

The experimental protocol was approved by the ethics committee of the Federal University of São Paulo in accordance with the Declaration of Helsinki (protocol # 1060/06). All subjects were informed of the aims and risks of the study, and their written informed consent was obtained. Twenty-two male, sedentary, healthy, elderly volunteers living independently in São Paulo/Brazil were recruited. The physical characteristics of the volunteers are presented in Table 1. All volunteers were submitted to a complete medical examination and received permission to train with a sports doctor prior to inclusion in the study. The exclusion criteria were the presence of cardiovascular pathologies or other diseases, including sleep disorders, preexisting or diagnosed during the clinical evaluation, that interfered with the response to training or study results. Additional exclusion criteria were the use medication or psychotherapeutic drugs for insomnia or other psychiatric disorders, working overnight and smoking.

2.2. Experimental design and training protocol

Twenty-two volunteers performed bouts of moderate exercise between 07:00 and 09:00. The training consisted of running for 60 min/day, 3 days/week for 24 week at a work rate equivalent to their ventilatory aerobic threshold. The environment was kept at a temperature of 23 ± 2 °C, with a humidity of $60 \pm 5\%$. Data were collected at 2 time points: at baseline (1 week before training began) and following 6 months of training. Baseline and post-intervention data were collected at the same time of day and, for the latter, after 24 h of rest to exclude any acute effects of exercise.

2.3. Testing protocol

2.3.1. Body composition

Total body mass and % fat were measured by whole-body plethysmography (air displacement plethysmography, BOD POD body composition system; Life Measurement Instruments, Concord, CA). Height was determined by a stadiometer. Body mass index (BMI) was calculated as the total body mass divided by height squared.

2.3.2. Ventilatory threshold and maximal oxygen consumption

The maximal oxygen consumption (VO_2 max) and ventilatory threshold for each volunteer were determined using an incremental exercise test on a treadmill. An initial velocity was set at 2.5 km/h, and the speed was increased by 1.0 km/h per minute until voluntary exhaustion. Expired gas was collected at the end of each stage

to determine the aerobic threshold. Respiratory and metabolic variables were obtained for each breath by measuring gaseous respiratory exchanges using a metabolic system (COSMED PFT4, Rome, Italy). After testing, invalid data were discarded, and analysis was performed after 20 s. The test yielded the following variables: VO_2 max, ventilator anaerobic threshold (VATI), heart rate at VATI, and threshold load (kilojoules). The criteria to determine the oxygen consumption at VATI followed those proposed by Wasserman et al. [18]: (1) an exponential increase in ventilation; (2) an abrupt increase in respiratory quotient (R); (3) a systematic increase in oxygen ventilator equivalent without a change in PEI or CO_2 equivalent; and (4) an increase in exhaled fraction of O_2 ($\text{FeOV}\%$). The VATI equivalent was defined as the state in which oxygen consumption was between 60% and 70% of VO_2 max and in which the patient was at 70–80% of heart rate reserve and between the values 12 and 14 on the Borg scale of perceived exertion (moderate aerobic exercise).

2.3.3. Polysomnographic recordings

Polysomnographic recordings were performed according to Rechtschaffen and Kales [19], and electrode placement was performed according to the 10–20 system. 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 recordings were included: electroencephalogram (C3–A2, C4–A1, O2–A1), electrooculogram, chin and tibial electromyograms, electrocardiogram, airflow (thermal sensor), thoracic–abdominal movements, a microphone placed on the lateral neck to detect snoring, pulse oximetry, and body position. Thirty-second epochs were staged according to standard criteria and visually inspected by the sleep specialist. 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.

2.4. Medical outcomes study SF-36 questionnaire

The SF-36 is a multidimensional questionnaire that covers eight components: physical functioning, role limitations due to physical and emotional health problems, social functioning, vitality, general health perception, body pain, and mental health. All scores ranged from 0 to 100, with a higher score indicating a better quality of life [38]. The Geriatric Depression Scale (GDS) was also used to measure depression. The GDS is a 30-item questionnaire in which participants are asked to respond by answering yes or no in reference to how they felt over the past week [39].

2.4.1. Blood collection and cytokine determination

Blood samples (20 ml) were collected from the antecubital vein into sterile tubes containing heparin and were taken before training, 24 h after the last exercise session and after a 12 h fast. Blood samples were centrifuged at $650 \times g$ for 15 min, and plasma samples were stored at -80 °C. To eliminate inter-assay variance, all samples were analyzed in identical runs resulting in an intra-assay variance of $<7\%$. For each sample, the plasma concentrations of interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-10 (IL-10), tumor necrosis factor- α (TNF- α) and plasminogen activator inhibitor type-1 (PAI-1) were assessed by ELISAs using commercial kits (R&D

Table 1

Individual physiological and anthropometric characteristics of the volunteers before and after training.

	Before	6 Months	Δ (%)
Age (years)	71.27 \pm 0.82		
Height (m)	1.71 \pm 0.05		
Weight (kg)	71.40 \pm 8.34	67.68 \pm 8.37	–4.45
BMI (kg/m^2)	25.21 \pm 3.76	25.58 \pm 3.59	+1.60
VO_2 max ($\text{ml}/\text{min}/\text{kg}$)	28.10 \pm 4.57	32.49 \pm 4.93 ^a	+15.0
HR max (b/min)	149.14 \pm 12.28	155.06 \pm 11.93	+4.0
Speed max (km/h)	6.00 \pm 0.75	7.11 \pm 0.69 ^a	+18.5

^a Difference in relation to before, $p < 0.05$.

Systems®, São Paulo, Brazil). C-reactive protein (CRP) was also assessed using a commercial kit (Bioclin®, São Paulo, Brazil).

2.4.2. Statistical analyses

All results are presented as the mean \pm standard deviation. Data were evaluated using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). Significant differences were determined by paired T-tests with significance set at $p < 0.05$.

3. Results

The individual physiological and anthropometric characteristics of the volunteers before training are described in Table 1. Additionally, Table 1 shows that 6 months of moderate aerobic training improved aerobic capacity as demonstrated by an increase in VO_2 max and an increase in maximal velocity in a maximal test ($p < 0.0001$), relative to pre-training values ($p < 0.003$).

Table 2 shows the polysomnography data. REM latency was reduced after 6 months of training ($p < 0.02$) compared with values obtained prior to training. Although there was also a decrease in awake time after 6 months of training ($p < 0.05$), the others parameters from the polysomnography were not different, as shown in Table 2.

Training caused a reduction in plasma concentrations of IL-6 ($p < 0.0001$) and an increase in IL-10 ($p < 0.0001$). Additionally, the TNF- α concentration decreased after training when compared with baseline values ($p < 0.0001$). In addition to training-induced changes in IL-10 and TNF- α , the TNF- α /IL-10 ratio decreased relative to baseline levels ($p < 0.0001$), as is shown in Table 3. There were no differences in the plasma concentrations of CPR, IL-1, and PAI-1. Table 4 reports the results from the geriatric scale and quality of life questionnaire. The geriatric scale was reduced after exercise training (25%; $p < 0.05$) and an increase in quality of life was observed (7%; $p < 0.05$) when compared to values obtained prior to training.

Table 2
Polysomnographic parameters before and after training.

	Before	6 Months	Δ (%)
Total sleep time (min)	324.88 \pm 66.86	339.76 \pm 42.35	+4.5
Sleep efficiency (%)	75.56 \pm 13.04	80.19 \pm 10.47	+6.1
Sleep latency (min)	13.43 \pm 10.25	16.06 \pm 8.18	+19.5
REM sleep latency (min)	81.68 \pm 30.66	64.63 \pm 17.03 ^a	-20.8
Time of awake (min)	78.60 \pm 33.25	60.53 \pm 24.19 ^a	-21.5
Stage 1	6.45 \pm 4.92	5.77 \pm 3.36	-10.5
Stage 2	59.18 \pm 9.74	60.10 \pm 9.17	+1.5
Stage 3	3.93 \pm 2.11	3.68 \pm 2.29	-6.36
Stage 4	9.94 \pm 1.25	10.02 \pm 6.98	+0.8
% REM	14.23 \pm 6.73	14.31 \pm 7.78	+0.56

^a Difference in relation to before, $p < 0.05$.

Table 3
Plasma parameters before and after training.

	Before	6 Months	Δ (%)
CRP (g/l)	0.36 \pm 0.07	0.28 \pm 0.03	-22.2
IL-1 (pg/ml)	0.91 \pm 0.15	1.06 \pm 0.19	+16.48
IL-6 (pg/ml)	151.36 \pm 19.83	94.71 \pm 13.56 ^a	-37.42
IL-10 (pg/ml)	6.14 \pm 1.41	7.85 \pm 0.88 ^a	+27.85
TNF- α (pg/ml)	26.83 \pm 5.19	15.18 \pm 2.40 ^a	-43.42
TNF- α /IL-10	4.42 \pm 0.51	2.01 \pm 0.033 ^a	-54.52
PAI-1 (ng/ml)	31.24 \pm 3.55	27.62 \pm 4.40	-11.58

^a Difference in relation to before, $p < 0.05$.

Table 4
SF-36 questionnaire and geriatric scale before and after training.

	Before	6 Months	Δ (%)
Geriatric scale	6.79 \pm 3.92	5.16 \pm 3.75 ^a	-25
SF-36 CF	87.25 \pm 12.62	92.50 \pm 7.69 ^a	+7
SF-36 LAF	93.18 \pm 15.78	86.25 \pm 30.86	+8
SF-36 PAIN	80.55 \pm 19.61	76.15 \pm 27.86	-5
SF-36 EGS	77.45 \pm 16.03	75.40 \pm 19.54	-2
SF-36 V	78.41 \pm 13.57	79.50 \pm 14.04	+1
SF-36 AS	88.64 \pm 15.86	88.13 \pm 19.23	-0.6
SF-36 LAE	78.75 \pm 33.42	86.66 \pm 25.14	+10
SF-36 SM	81.09 \pm 13.48	83.80 \pm 17.63	+3
SF-36 Median	83.24 \pm 10.86	83.55 \pm 13.67	+0.4

^a Difference in relation to before, $p < 0.05$.

4. Discussion

Sleep-related disorders are frequent in the general population, particularly in older individuals, and it is possible that sleep complaints may be promoted by an increased presence of medical and psychosocial comorbidities in this population [20].

Physical exercise has been suggested to be an important strategy for the treatment of sleep disorders. Several studies have demonstrated that moderate exercise training can partially reduce sleep complaints [10,13,16,21–24]. Therefore, the objective of this study was to assess the effect of training on sleep quality in elderly individuals and to determine the relationship between sleep and pro-inflammatory cytokine levels.

The subjects completed 6 months (24 weeks) of moderate exercise training. Each exercise session consisted of moderate exercise on a treadmill for 60 min/day, 3 days/week at a workload similar to the ventilatory aerobic threshold recently recommended by the American College of Sports Medicine (ACSM) [25]. The ACSM recommendations have determined that this type of training regimen is effective because it yields a significant increase in aerobic capacity compared with aerobic capacity before training. Our results demonstrate the effectiveness of this moderate training regimen and confirm the adaptations of improved aerobic capacity and fitness as indicated by an increase in VO_2 max (15.6%) and maximal speed during the incremental exercise test on a treadmill (18.5%).

Moderate exercise training has been described as an important tool to prevent or treat numerous pathological conditions, including certain aspects of senescence [21,26] and sleep disturbance in older individuals. However, the mechanisms of action are not well understood [27].

The normal sleep-wake cycle is modulated by a wide variety of physiologic, psychological and environmental factors, including circadian factors. In regards to physiological regulation, many substances can affect sleep including substances from the immune response as well as cytokines that regulate inflammation, particularly IL-1 β , IL-6 and TNF- α [14,28]. An increase in pro-inflammatory cytokines have been shown to induce sleep, whereas an increase in anti-inflammatory cytokines can improve sleep patterns [29]. A recent study showed that sleep restriction can promote changes in cytokine profiles [30]. Therefore, an imbalance between pro- and anti-inflammatory cytokine signaling may be associated with a decline in health in older patients, leading to an increase in illnesses such as metabolic and cardiovascular diseases.

Older individuals may demonstrate elevated IL-1 β and TNF- α concentrations, both of which can increase NREM sleep by impairing a subset of sleep-related neurons in the preoptic area/basal forebrain. The administration of IL-1 β and TNF- α in the somatosensory cortex has been shown to increase slow waves during NREM sleep [10,11,28].

Six months of training promoted a partial recovery of time spent awake, which was decreased 21% compared with pre-training values. This result may be mediated by changes in IL-6 levels because previous studies suggest an effect of IL-6 and TNF- α on periods of wakefulness. Increases in IL-6 levels have a bi-phasic effect on sleep: an initial increase in the amount of time spent in non-REM (NREM) sleep followed by NREM sleep impairments and increased time awake [31]. Additionally, elevated TNF- α levels are associated with excessive daytime sleepiness and nocturnal sleep disturbances [32]. After 6 months of training, a decrease in the wakefulness period was associated with a decrease in plasma concentrations of IL-6 and TNF- α and a 54% reduction in the TNF- α /IL-10 ratio, which suggests that a reduction in inflammation can influence sleep.

Other changes in sleep caused by aging include a decrease in total sleep time (TST) and a reduction in sleep efficiency [2,33]. The training regimen promoted recovery in these parameters, as indicated by an increase in TST (15 min or 4.5%) after 6 months of training. It is possible that an increase in TST was limited by sleep efficiency. TST has been shown to decrease with age: 45-year-olds demonstrate approximately 85% sleep efficiency, whereas in 70-year-olds, sleep efficiency decreases to 79%. At the beginning of this study, sleep efficiency in our volunteers was $75.56 \pm 13.04\%$, values considered normal for older individuals [2]. However, sleep efficiency was 6.1% higher after 6 months of training. Our data supports earlier studies suggesting that the practice of regular exercise can be important for attenuating the effects of aging on sleep [13,27]. Additionally, moderate training is important as an additional strategy for the treatment of adverse age-associated changes in sleep patterns. Furthermore, it is possible that the effects of training may be more pronounced in individuals with sleep complaints that are older than those included in our study.

Several studies have demonstrated that older individuals spend a smaller percentage of time in REM sleep and a higher percentage of time in light sleep (stages 1 and 2 sleep) [34]. Stage 1 is a transition between wakefulness and sleep. Discrete changes in physiological and biochemical activities (i.e., decreases in body temperature) that occur in stage 2 may contribute to frequent nocturnal awakenings, non-restorative sleep, cognitive decline, obesity, reduced lean body mass, and impaired exercise response, all of which are more frequent in older individuals [33]. Our results support a previous study showing that 6 months of moderate exercise training was not sufficient to promote changes in stages 1 and 2 sleep and caused an increase of only 0.56% in percent REM sleep, which indicates that the improved cognition induced by physical training was not a consequence of changes in sleep stage.

Slow wave sleep is associated with the homeostatic functions of sleep [33,35]. No changes in the amount of slow wave sleep were found after 6 months of training. It is possible that the moderate training protocol was not sufficient to induce the depletion of energy stores required to modify stages 3 and 4 sleep, which would be important for restored homeostasis.

Moderate exercise training has been recommended as an anti-inflammatory therapy [36]. In support of previous work, our results demonstrate that training causes a decrease in TNF- α (43%) and IL-6 (37%) levels but does not alter the levels of IL-1 β and CRP, which suggests that moderate training can reduce inflammation in elderly individuals. The training-induced changes associated with an improvement in the inflammatory profile, demonstrated by a significant decrease in the TNF- α /IL-10 ratio, were sufficient to improve global sleep phases, but because NREM sleep was not affected by training, they were not able to alleviate all sleep complaints.

In agreement with Wu et al. [37], other factors can also influence sleep, such as restless legs syndrome, major depressive disorder, anxiety disorder, use of tricyclic antidepressant, presence of heart

disease, cancer, chronic pain, gender, alcohol dependence, bipolar disorder, use of over-the-counter sleeping pills, and narcotic analgesics. A limitation of our study was that food intake was not controlled during the study, although the maintenance of identical eating habits was recommended. We also did not include a control group.

Our study is the first to evaluate the association between inflammation, sleep patterns, and quality of life in older individuals following a period of moderate exercise training. Our results demonstrate that moderate exercise training may improve aspects of adverse sleep in older individuals such as REM sleep latency, time of wakefulness, and sleep efficiency. Furthermore, these improvements can be partially modulated by changes in the cytokines profile and by a reduction in inflammation.

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