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Aerobic exercise does not change C-reactive protein levels in non-obese patients with obstructive sleep apnoea

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Abstract
The aim of this study is to evaluate the effects of a 2-month aerobic exercise training programme on C-reactive protein (CRP) levels in non-obese patients with obstructive sleep apnoea. Twenty non-obese and sedentary adult male volunteers underwent polysomnography (PSG) to assess their sleep parameters. After the PSG analysis, the subjects were divided into two groups (CTRL, control and OSA, obstructive sleep apnoea). Twenty-four sessions of aerobic exercise were performed, and PSG was repeated on the night that followed the last physical training session (24th). Blood samples were collected for CRP analysis before the first exercise session and after the last session. The OSA group demonstrated a reduction in sleep latency (SL) after 2 months of physical exercise, and 80% of them showed a lower apnoea-hypopnoea index (AHI), although this difference was not statistically significant. The differences between the CRP values for the CTRL and OSA groups were also not statistically significant at baseline or after 2 months of physical exercise. Furthermore, there was no correlation between the CRP levels and body mass index (BMI) in the two groups assessed. Our results suggest that in non-obese patients with OSA, CRP levels were normal and did not change after 2 months of aerobic exercise training.

Keywords: C-reactive protein, physical exercise, obstructive sleep apnoea

Introduction
C-reactive protein (CRP) is a specific marker found in the blood that is synthesised by the liver (Pepys & Hirschfield, 2003) in response to factors released by fat cells (adipocytes) (Lau, Dhillon, Yan, Szmitko, & Verma, 2005). Its concentration can be altered by circumstances that trigger inflammatory processes (Cummings, King, Mainous, & Geesey, 2006; Ridker, Cushman, Stampfer, Tracy, & Hennekens, 1998). A positive association between higher levels of CRP and greater body mass index (BMI) (Haverkate, Thompson, Pyke, Gallimore, & Pepys, 1997) has been shown, consistent with obese individuals being in a chronic state of mild systemic inflammation (Visser, Bouter, McQuillan, Wener, & Harris, 1999). Approximately 70% of individuals with obstructive sleep apnoea (OSA) are obese (Malhotra & White, 2002), and it has been suggested that the severity of OSA syndrome correlates with the BMI classification (Vgontzas, 2008). However, in some studies, patients with OSA showed elevated levels of CRP, TNF-α and IL-6, independent of obesity. These factors are associated with sleepiness, fatigue and the development of various metabolic and cardiovascular diseases (Shamsuzzaman et al., 2002; Vgontzas et al., 2000; Yokoe et al., 2003).

According to Smith, Dykes, Douglas, Krishnawamy, and Berk (1999), long-term physical exercise can significantly reduce the levels of CRP and inflammatory cytokines, suggesting an anti-inflammatory benefit of exercise that may...
contribute to the prevention of cardiovascular diseases. Kasapis and Thompson (2005) have also suggested that physical exercise produces a short-term inflammatory response, whereas in the long term, it has an anti-inflammatory effect. Several studies have examined the effects of physical exercise on objective and subjective sleep parameters, quality of life and mood state, but these studies did not evaluate the effects of this treatment on the CRP values of OSA patients (Ackel-D’Elia et al., in press; Giebelhaus, Strohl, Lormes, Lehmann, & Netzer, 2000; Kline et al., 2011a, 2011b; Norman, Von Essen, Fuchs, & McElligott, 2000; Sengul, Ozalevli, Oztura, Itil, & Baklan, 2009; Ueno et al., 2009).

The published literature is unclear regarding whether higher values of CRP are more closely associated with OSA or obesity, or if both conditions are associated with the biomarker. Specifically, it has not been conclusively determined whether higher levels of CRP are observed in non-obese OSA patients. Barcelo et al. (2004) suggested that increased CRP levels may be more highly correlated with obesity than with apnoea and showed that CRP levels did not change after treatment with continuous positive airway pressure (CPAP) in non-obese individuals. However, the effects of physical exercise on CRP levels in non-obese OSA patients have not been previously studied.

We hypothesised that physical exercise would reduce CRP levels in non-obese patients with OSA. Thus, the objective of this study was to evaluate the effects of a 2-month aerobic exercise training programme on CRP levels in non-obese patients with obstructive sleep apnoea.

**Methods**

**Subjects**

For this study, 20 adult male volunteers, aged 36.85 ± 11.00 years, were included. The volunteers were sedentary (classified by the physiological index, \(VO_2\) max) (Wilmore & Costill, 2005). No abnormalities in the clinical and laboratory exams, including resting and stress electrocardiograms, were observed that would contraindicate the practice of physical exercise or be expected to increase the levels of CRP. The exclusion criteria were BMI >30 and the presence of cardiovascular pathologies or other diseases (pre-existing or diagnosed during the clinical evaluation) that would interfere with the response to training or the study results.

A total of 32 adult male volunteers were selected in accordance with the inclusion criteria of the present study. Twenty volunteers completed the study: 10 of 15 volunteers and 10 of 17 volunteers completed the study in the Control (CTRL) and OSA groups, respectively. The main reasons for patients drop-out were lack of interest during the study (5 patients), professional problems (5 patients) and health problems (2 patients).

This study was approved by the Research Ethics Committee of the Federal University of São Paulo (1240/08).

The volunteers were divided into CTRL and OSA groups after conducting polysomnography (PSG) to assess their sleep parameters. The CTRL group was composed of 10 individuals without any type of sleep disorder and the OSA group was composed of 10 individuals who had Epworth Sleepiness Scale values ≥10 (Johns, 1991), snoring along with an apnoea-hypopnoea index (AHI) >5 events/h, or >15 AHI events/h (AASM, 2005).

**Experimental design**

Upon completion of the adaptation and baseline PSG, the volunteers completed a maximum effort test (MET). Twenty-four sessions of aerobic exercise were performed (three 40-minute sessions per week), and a repeat PSG test was performed on the night after the last physical training session. Blood samples were collected for CRP analysis before the first exercise session and after the last session (24th).

**Polysomnography**

Overnight PSG was performed using an EMBLA digital system (EMBLA S7000, Embla Systems Inc., CO, USA). Electrodes were placed according to the international 10-20 system (Jasper, 1958). The following variables were monitored: electroencephalogram (four channels: C3-A2, C4-A1, O1-A2, O2-A1), electrooculogram (two channels: LOC-A2, ROC-A1), electromyogram (two channels: submental and anterior tibialis muscles) using surface electrodes, ECG (one channel), snoring and body position were detected with EMBLA sensors. Airflow was detected by with a thermocouple and a nasal pressure flow transducer. Respiratory effort of the chest and abdomen were monitored by inductance plethysmography. Oxyhemoglobin saturation (SpO2) and pulse-rate were recorded with a pulse oximetre. Sleep stages and events were manually scored using the international rules (AASM, 2005; ASDA, 1992, 1993; Rechtschaffen & Kales, 1968). The following parameters were evaluated: total sleep time (TST), sleep efficiency (SE), sleep latency (SL), Rapid Eye Movement (REM) stage, REM latency, arousal index, wake after sleep onset, non-REM sleep stages 1 and 2 and slow-wave sleep and AHI.
CRP analysis

The nephelometric technique was used for the analysis of CRP. This procedure measures high-sensitivity CRP (HS-CRP) with a sensitivity of 1 mg/L and a reference value of 0.5 mg/dL.

Maximum effort test

The MET was performed to determine the appropriate physical training regimen (ventilatory threshold 1, VT1). The test was performed in the same environment and with the same treadmill (Life Fitness® 9700 HR) used for training. The MET protocol consisted of a 2-min warm-up at a speed of 4 km/h, after which the speed was increased by 1 km/h each minute until exhaustion. A fixed slope of 1%, simulating the physical stress of open spaces, was used throughout the test (Jones & Doust, 1996).

Training programme

Twenty-four sessions of aerobic exercise on a treadmill were performed over a period of 2 months. Specifically, the subjects exercised three times per week (on alternate days). All sessions were performed in the morning and lasted 40 minutes. The intensity of the aerobic exercises was monitored individually to maintain the individual's heart rate at the VT1 intensity as defined by the MET test. Before the aerobic exercises, all volunteers stretched their upper and lower limbs and walked (5 km/h) on a treadmill for 5 minutes. Following the aerobic exercises, the volunteers reduced the intensity of exercise to recover. Five volunteers (15.62%) were excluded from the study due to lack of adherence to the physical exercise programme.

Statistical analysis

The data were analysed using Statistica for Windows 7.0 (StatSoft, Inc.). After confirming the normal distribution of the data, Student’s t-test was used to evaluate baseline characteristics of the two groups. In addition, the sleep patterns were analysed by two-way ANOVA followed by the Duncan test when appropriate. The Kruskal-Wallis test was used to compare the values of CRP before and after the physical exercise training. Pearson’s correlation was used to analyse the association between BMI and CRP level. The significance level was set at $p < 0.05$ for all tests.

Results

Table I shows the baseline physical characteristics of the CTRL and OSA groups. Lower values for age ($p = 0.08$) and triglycerides ($p = 0.07$) were observed in the CTRL group, although the differences in these baseline values were not statistically significant. Moreover, no significant differences were demonstrated in BMI after 2 months of physical exercise in either group (data not shown).

Among the sleep parameters, significant differences between the baseline and post-physical exercise values were observed for SE, SL and REM (%). Post hoc analysis revealed that SE and REM (%) were significantly increased in the CTRL group after physical exercise, and SL was significantly reduced after physical exercise in the OSA group.

A significant difference in the AHI between the CTRL and OSA groups was observed. Post hoc analysis revealed that the OSA group had a significant increase in the AHI compared to the CTRL group in both the baseline and after physical exercise (Table II).

After physical exercise, 80% of OSA group showed lower AHI, however, statistical differences for AHI were not observed. (Table II and Figure 1). The differences in the CRP values for the CTRL and OSA groups were not statistically significant at baseline or after 2 months of physical exercise (Figure 2). There was no correlation between the CRP levels and BMI in these subjects.

Discussion

In this study, the effects of aerobic exercise on CRP in non-obese patients with obstructive sleep apnoea were evaluated. No reductions in CRP levels were observed after 2 months of aerobic exercise training in non-obese patients with OSA compared to the CTRL subjects. Moreover, no correlation between CRP levels and BMI in the two groups was observed.

Increases in CRP levels can be significantly related to the severity of OSA syndrome (Shamsuzzaman et al., 2002); that is, a higher AHI in OSA patients is associated with greater inflammation (Kokturk, 2011).

Table I. Baseline physical characteristics of CTRL and OSA groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CTRL ($n = 10$)</th>
<th>OSA ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.20 ± 10.19</td>
<td>40.50 ± 10.41</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>27.54 ± 1.88</td>
<td>25.98 ± 3.35</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>184.44 ± 37.02</td>
<td>211.00 ± 39.65</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>44.11 ± 10.22</td>
<td>46.60 ± 7.96</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>116.55 ± 32.99</td>
<td>129.60 ± 32.92</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>118.44 ± 43.08</td>
<td>174.00 ± 77.16</td>
</tr>
<tr>
<td>Total Protein (g/dL)</td>
<td>7.54 ± 0.43</td>
<td>7.25 ± 0.48</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.28 ± 0.16</td>
<td>0.22 ± 0.16</td>
</tr>
<tr>
<td>$\dot{V}O_2$ Max (ml/kg/min)</td>
<td>39.33 ± 6.96</td>
<td>39.68 ± 7.63</td>
</tr>
</tbody>
</table>

Notes: Mean ± SD; Student’s t-test.

$\dot{V}O_2$ Max, maximum oxygen consumption; CTRL, control; OSA, obstructive sleep apnoea.
Ciftci, Mollarecep, & Ciftci, 2005). The population evaluated in this study had moderately severe OSA (mean value) in the baseline condition, and the majority of OSA patients showed a lower AHI after the training protocol.

Barceló et al. (2004) reported elevated CRP levels in obese patients with OSA compared to non-obese patients with OSA prior to intervention. However, these authors also showed that the CRP levels did not change after CPAP treatment in either obese or non-obese individuals.

Michigan, Johnson, and Master (2011), in a recent review, discussed the lack of a consensus in the scientific literature regarding the relationship between exercise and CRP levels. The potential anti-inflammatory effects of physical exercise might be explained by the increased protein synthesis and fat loss that occurs during this intervention.

In the present study, the OSA patients were non-obese and presented CRP values within normal ranges at baseline. We believe this may explain the failure to achieve the expected reduction in CRP levels after the training protocol.

Regarding the sleep parameters, effects of physical exercise were observed for SE and REM (%) in the CTRL group and observed for SL in the OSA group. However, we did not observe a statistically significant effect of physical training on the AHI in the OSA group. It is possible that 2 months of training was insufficient to cause these changes because previous studies that showed a reduction in the AHI involved physical training for at least 3 months.

Sengul et al. (2009) showed significant improvements in AHI in OSA patients after 3 months of breathing exercises and aerobic exercises, three times per week. Similarly, Ueno et al. (2009) showed that 4 months of aerobic exercise three times per week improved the AHI, the minimum SpO2 and the amount of stage 3–4 sleep in OSA patients with heart failure.

Recently, Kline et al. (2011a, 2011b) observed a significant reduction in the AHI and the oxygen desaturation index without a significant body weight reduction after 3 months of moderate-intensity exercise (aerobic activity and resistance training).

### Table II. Analysis of the effect of 2 months of aerobic exercise on the sleep patterns in the CTRL and OSA groups

<table>
<thead>
<tr>
<th>Sleep parameter</th>
<th>CTRL</th>
<th>OSA</th>
<th>ANOVA F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Group</td>
<td>Interaction</td>
<td></td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>369.85 ± 12.57</td>
<td>376.98 ± 9.68</td>
<td>0.27 1.87 0.02</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>87.83 ± 2.81</td>
<td>93.68 ± 1.01</td>
<td>4.32* 0.24 4.35*</td>
</tr>
<tr>
<td>Sleep latency (min)</td>
<td>7.88 ± 3.12</td>
<td>2.88 ± 1.39</td>
<td>8.44* 0.28 0.02</td>
</tr>
<tr>
<td>REM latency (min)</td>
<td>71.45 ± 8.31</td>
<td>82.67 ± 16.03</td>
<td>1.01 1.16 3.03</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>4.34 ± 1.18</td>
<td>3.32 ± 0.64</td>
<td>1.84 0.21 0.79</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>55.74 ± 2.38</td>
<td>53.81 ± 1.93</td>
<td>0.05 0.13 0.73</td>
</tr>
<tr>
<td>Slow-wave sleep (%)</td>
<td>19.77 ± 2.39</td>
<td>18.84 ± 1.49</td>
<td>7.13 0.05 0.27</td>
</tr>
<tr>
<td>REM (%)</td>
<td>18.31 ± 1.52</td>
<td>23.98 ± 2.47</td>
<td>6.11* 0.09 3.79</td>
</tr>
<tr>
<td>Arousal index</td>
<td>12.95 ± 4.31</td>
<td>12.54 ± 2.30</td>
<td>0.01 2.54 0.03</td>
</tr>
<tr>
<td>AHI (events/hour of sleep)</td>
<td>3.47 ± 0.54</td>
<td>10.07 ± 4.18</td>
<td>0.73 9.19 2.66</td>
</tr>
</tbody>
</table>

Note: Values are presented as mean ± SE. P ≤ 0.05 comparing groups for the *time factor, "group factor and "interaction (two-way ANOVA followed by the Duncan test). Comparison of groups by the post hoc test for the a-b-c time factor and the d-group factor.

**Figure 1.** Changes in the individual apnoea-hypopnoea index before and after 2 months of physical exercise, using obstructive sleep apnoea classification (mild, moderate and severe) in OSA group.

**Figure 2.** C-reactive protein levels in the CTRL and apnoea groups, before and after 2 months of aerobic exercise (Kruskal-Wallis test). Values are presented as median. CTRL, control; OSA, obstructive sleep apnoea.
Although we did not observe significant difference for the AHI (mean value) after physical training in this study, the AHI improved for 80% of the OSA subjects after treatment. Moreover, the severity of OSA (mild, moderate, severe) was reduced in some of these patients after the exercise intervention.

Moreover, controversial studies have analysed the effects of physical exercise associated with CPAP. Netzer et al. (1997) evaluated the effects of a 6-month period of physical exercise (twice a week for 2 hours each time) in 11 patients with mild to severe OSA. The authors did not detect any significant differences in basal SpO₂ or mean SpO₂. However, the exercise significantly decreased the respiratory disturbance index without significantly affecting the REM-sleep portion of the TST. A significant increase in the TST itself was also observed in this study. Norman et al. (2000) observed improvements in the AHI, the TST, the SE and the number of awakenings in mild to moderate OSA patients after 6 months of a supervised exercise programme. However, 5 of the 9 patients concurrently used regular CPAP therapy, but the analysis did not address this possible confounding factor. In another study, patients with OSA were treated with CPAP and enrolled in a 6-month period of supervised physical exercise twice a week. These patients exhibited a significant decrease in the respiratory disturbance index, from 32.8 to 23.6. However, no significant differences were detected in the minimum SpO₂, mean SpO₂, REM-sleep portion of TST, NREM sleep or TST itself (Giebelhaus et al., 2000). In contrast, Ackel-D’Elia et al. (in press) did not observe differences for sleep parameters after 2 months of an exercise programme of one hour of aerobic exercise three times per week in OSA patients undergoing CPAP therapy.

Although we believe that this study provides relevant findings, the small number of volunteers evaluated is a limitation of the study. Nevertheless, the strengths of this research are the PSG assessment, which is considered the gold standard for sleep analysis, in addition to the systematic evaluation of physical training in patients not treated with CPAP. More importantly, this study evaluated the effect of the physical training on CRP values in OSA patients.

In conclusion, our results suggest that in non-obese patients with OSA, CRP levels were normal and did not change with physical exercise.

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