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ORIGINAL ARTICLE

Oxidative Stress and Inflammation after Continuous Positive Airway Pressure Therapy in Patients with Severe Obstructive Sleep Apnea

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ABSTRACT

Background: It has been demonstrated that moderate to severe obstructive sleep apnea (OSA) leads to generation of reactive oxygen species and inflammation. We evaluated whether continuous positive airway pressure (CPAP) treatment progressively improves oxidative stress and inflammation, and whether an association exists in severe OSA patients between severity of OSA and biomarkers of oxidative stress and inflammation.

Methods: Forty patients with severe OSA (apnea hypopnea index, AHI: 37.8 $\pm$ 5.8 /h) that were newly diagnosed using polysomnography were recruited. Patients received CPAP treatment for six months. Patients were assigned to CPAP and non-CPAP treatment groups in equal numbers. The levels of malondialdehyde (MDA), alanine aminotransferase (ALT), aspartate aminotransferase (AST), high sensitivity C-reactive protein (hs-CRP), neutrophils to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR) were measured prior to and after three and six months of therapy.

Results: AHI was positively correlated with MDA ($r = 0.4728$, $p < 0.01$), ALT ($r = 0.6081$, $p < 0.001$), AST ($r = 0.6299$, $p < 0.001$), NLR ($r = 0.3943$, $p < 0.05$), PLR ($r = 0.3319$, $p < 0.05$), and hs-CRP ($r = 0.5728$, $p < 0.001$). In the CPAP but not in non-CPAP treatment group, MDA, AST, NLR, PLR, and hs-CRP levels ($p < 0.001$), and ALT ($p < 0.05$) levels were improved after three and six months of treatment. After six months, MDA levels decreased further compared to MDA levels at three months, and this decrease was significant ($p < 0.001$).

Conclusion: Our study demonstrates that CPAP therapy in severe OSA patients produces clinical benefits by improving oxidative stress and inflammation progressively, and that severity of OSA is correlated with oxidative stress and inflammation.

Keywords: obstructive sleep apnea, continuous positive airway pressure, oxidative stress, liver inflammation, systemic inflammation

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INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by the breathing interruptions or awakenings due to gasping or choking in the presence of at least five obstructive respiratory events (apneas, hypopneas, or respiratory related arousals) per hour of sleep (Epstein et al., 2009). It is likely that a multifactorial process is present, including arousal, autonomic nervous system imbalance, ischemic-reperfusion injuries induced oxidative stress, and inflammation (Carpagnano, Lacedonia, & Foschino-Barbaro, 2011).

Repetitive oscillations in oxygen levels may provoke increased oxidative stress, via ischemia reperfusion injury (Tichanon et al., 2016). Malondialdehyde (MDA) is commonly known as a marker of oxidative stress (Luangaram, Kukongviriyapan, Pakdeechote, Kukongviriyapan, & Pannangpetch, 2007). Previous studies on this are also ambiguous, showing either a significant increase in oxidative stress (Celec et al., 2012; Wang, Li, Xie, & Zhang, 2010) or no significant increase (Yamauchi et al., 2005) in OSA patients.

OSA causes accumulation of fatty acids in the liver and inflammation as a result of recurrent nocturnal hypoxia, insulin resistance, oxidative stress and dysregulation of adipokines. Previous studies show that apnea hypopnea index (AHI) and apnea index are positively correlated with alanine aminotransferase (ALT) and aspartate aminotransferase (AST) where as lowest oxygen saturation (SpO_2), a consequence of nocturnal hypoxia, shows a negative correlation with ALT and AST (Aron-Wisnewsky, Clement, & Pépin, 2016; Cakmak et al., 2015). The authors concluded that OSA patients progressively develop nonalcoholic liver fatty liver disease (NAFLD). Jouët P and coworkers reported that morbidly obese OSA patients had elevated levels of liver enzymes (Jouët et al., 2007). On the other hand, other studies have shown no adverse effect of OSA on the liver enzymes (Daltro et al., 2010; Kallwitz, Herdegen, Madura, Jakate, & Cotler, 2007).

Recently, neutrophil to lymphocyte ratios (NLR) and platelet to lymphocyteratios (PLR) have emerged as potential new biomarkers that indicate the presence of systemic inflammation (Kivanc & Kulaksizoglu, 2017) as well as high sensitivity C-reactive protein (hs-CRP), which is an acute-phase protein that is generated in the liver (Kim et al., 2016). Several studies have examined relationships between hs-CRP, NLR, and PLR in OSA patients with different severities. Either significant increases in inflammation biomarkers (white blood cell count, WBC) (Calvin, Albuquerque, Lopez-Jimenez, & Somers, 2009), hs-CRP (Kim et al., 2016) and PLR (Kivanc & Kulaksizoglu et al., 2017) or no significant increase (Koseoglu et al., 2015) have been found in OSA patients.

Continuous positive airway pressure (CPAP) is the gold standard treatment for OSA (McDaid et al., 2009). Previous studies show a significant decrease in oxidative stress following three months of CPAP treatment in moderate to severe OSA patients (Celec et al., 2012; Hernandez, Abreu, Abreu, Colino, & Jimenez, 2006; Tichanon et al., 2016). However, one study found no evidence of increased MDA levels in moderate to severe OSA patients after withdrawal CPAP therapy for two weeks (Stradling et al., 2015). A single night of CPAP treatment was sufficient to reduce AST levels, and a sustained improvement was observed after one to six months of CPAP treatment (Chin et al., 2003). CPAP treatment also reduced ALT levels (Shpirer, Copel, Broide, & Elizur, 2010; Toyama et al., 2014). Kohler and coworkers have reported a decrease in inflammatory markers after two weeks of CPAP therapy compared to a control group (Kohler et al., 2011). However, another study found no significant changes in inflammation parameters, e.g. WBC, hs-CRP, interleukin-6 (IL-6), tumor necrosis factors-alpha) in patients with OSA after two months of CPAP therapy (Kritikou et al., 2014).

This study aimed to evaluate the association between severity of OSA and oxidative stress and inflammation biomarkers, and whether CPAP treatment improves oxidative stress, liver inflammation, and systemic inflammation.

METHODS

Study subjects

This study was non-randomized and open-labeled. Forty severe OSA patients who were newly diagnosed by

medical specialists using polysomnography (PSG) within the month preceding the beginning of the study were recruited from the Sleep Disorder Clinic at Srinagarind Hospital, Khon Kaen, Thailand between July 2016 and May 2017. Clinically, patients with an apnea–hypopnea index (AHI) > 30 per hour with no history of cardiovascular disease were studied. Patients with history of central sleep apnea, autoimmune conditions, diabetes mellitus, fatty liver disease, urinary tract infection, or symptoms of respiratory tract infection six weeks prior to the study were excluded. Patients chose to enroll in either the CPAP treatment (CPAP group, n = 20) or non-CPAP treatment group (n = 20). Patients received a general health care treatment program for OSA, including nasal spray for nasal allergies, and sleep hygiene education.

The purpose, benefits, and possible risks associated with the study were explained to the subjects and informed consent was obtained, in accordance with the Khon Kaen University Ethics Committee for Human Research (approval numbers HE591202).

Polysomnography

OSA patients underwent full-night PSG using a digital system at the Sleep Disorder Clinic, Faculty of Medicine (Srinagarind Hospital, Khon Kaen University). PSG was performed using a procedure described previously (Tichanon et al., 2016). The scoring apnea and hypopnea respiratory event parameters recommended by the AASM were performed. Apnea was defined as a decrease in amplitude of airflow of at least 90% for at least 10 seconds and continued respiratory effort. Similarly, hypopnea was defined as a reduction in airflow of at least 30% that coincided with a decrease in oxygen desaturation of at least 3% and/or an event associated with an arousal. The respiratory effort-related arousal (RERA) is defined as increased respiratory effort or flattening of the nasal pressure waveform, leading to an arousal in which the sequence of breaths does not meet the criteria for hypopnea. The respiratory disturbance index (RDI) is defined as the average number of respiratory disturbances (obstructive apneas, hypopneas, and RERA) per hour (Heinrich, Spiesshofer, Bitter, Horstkotte, & Oldenburg, 2015).

CPAP therapy and follow up

CPAP (DeVilbiss IntelliPAP Auto-Adjust, USA) was administered during sleep at night for at least five hours per night, for at least five days per week, and for 180 consecutive days. The patients came for a follow up visit every month, during which average hours of nightly use (h) and average days per week (days/week) of CPAP therapy for each patient were recorded from the CPAP device. The range of optimal CPAP pressure was adjusted manually each month if necessary.

Malondialdehyde (MDA)

The level of MDA was measured following previously described methods (Luangaram et al., 2007). MDA reacts with thiobarbituric acid in boiling water to form a colored complex called thiobarbituric acid-reactive substance (TBARS), which can be detected by a spectrophotometric assay. Plasma samples (150 μL) were treated with 10% TCA, 5mM EDTA, 8% SDS, and 0.6 μg/mL of BHT. The mixture was incubated for 10 minutes at room temperature, 0.6% TBA was added, and the mixture was boiled in a water bath for 30 minutes. After cooling to room temperature, the mixture was centrifuged at 10,000 ×g for five minutes. The absorbance of the supernatant was measured at 532 nm by a spectrophotometer. A standard curve was generated with appropriate concentrations of 1,1.3,3-tetraethoxypropane (0.3–10 μM).

Biochemical analyses

Blood samples were collected after an overnight fasting. All samples were investigated at Srinagarind Hospital, Khon Kaen University. A complete blood cell count was performed on Coulter LH 780 series automated blood cell counter (Beckman Coulter, USA), Liver enzymes (AST, ALT) levels were collected on Cobas 6000 analyzer series (Roche diagnotics, Switzerland) and hs-CRP levels were performed on Cobas e411 analyzer series (Roche diagnotics, Switzerland). NLR and PLR were obtained from the absolute neutrophil and platelet counts, respectively, divided by the absolute lymphocyte counts (Kivanc & Kulaksizoglu, 2017). All samples were processed by technicians blinded to the samples.

Statistical Analyses

Statistical analyses were performed using STATA version 13.0 (Stata Corp, College Station, TX). Data were expressed as mean and standard deviation (SD). The relationship between severity of OSA and inflammation and oxidative stress parameters were determined by linear regressions. An unpaired t-test was used to compare OSA patients treated with CPAP and non-CPAP groups with respect to anthropometric features, clinical characteristics, oxidative stress, and inflammation parameters on Day 0. A repeated-measures ANOVA was used to compare CPAP parameters, oxidative stress, and inflammation parameters between Day 0, 90, and 180 of CPAP therapy in both CPAP and non-CPAP groups. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 shows average normal ranges of baseline demographic data in 40 OSA patients. Forty five patients were initially recruited to the study. After recruitment, 24 patients chose to have a CPAP treatment and 21 chose a non-CPAP treatment. Two CPAP patients and one non-CPAP patient missed a follow up appointment. In addition, two CPAP patients dropped out due to lack of CPAP compliance. The remaining 20 patients in CPAP group and 20 patients in non-CPAP group were studied. There were six males and 14 females in CPAP group and nine males and 11 females in non-CPAP group. No significant differences in these demographic data between patients in CPAP and non-CPAP treatment groups were found. In CPAP group, an Epworth Sleepiness Scale improved after 90 (4.1 ± 2.2) and 180 (2.2 ± 1.1) consecutive days of CPAP treatment and Day 180 compared to Day 90 and Day 0 (15.6 ± 1.8) ($p < 0.01$).

PSG data for subjects in CPAP and non-CPAP treatment groups (Day 0) and CPAP parameters for subjects in the CPAP treatment group on Day 180 are

Table 1. Baseline demographic data in OSA patients (CPAP and non-CPAP treatment groups)

	CPAP (n = 20)	Non-CPAP (n = 20)
Age (years)	45.3 ± 10.5	48.4 ± 11.9
Gender (M/F)	6/14	9/11
Height (cm)	163.9 ± 6.2	163.2 ± 8.4
Weight (kg)	68.9 ± 10.3	69.0 ± 11.8
BMI (kg/m^2)	25.7 ± 3.7	25.9 ± 3.7
Neck circumference (cm)	34.9 ± 3.4	33.9 ± 4.1
Waist circumference (cm)	83.0 ± 10.6	86.3 ± 7.8
Hip circumference (cm)	94.9 ± 7.5	95.9 ± 7.0
Epworth sleepiness scale	15.6 ± 1.8	16.2 ± 1.5
Heart rate (/min)	82.7 ± 10.1	83.6 ± 11.1
Systolic BP (mm Hg)	124.9 ± 10.8	128.0 ± 11.7
Diastolic BP (mm Hg)	90.2 ± 11.2	84.5 ± 14.0
MAP (mm Hg)	101.7 ± 10.0	99.0 ± 11.6

Data are expressed as mean ± SD. OSA: obstructive sleep apnea, CPAP: continuous positive airway pressure, M: male, F: female, BMI: body mass index, BP: blood pressure, MAP: mean arterial pressure

Table 2. Polysomnographic data prior to CPAP therapy in OSA patients(CPAP and non-CPAP treatment groups)

		CPAP (n = 20)		Non-CPAP (n = 20)
Polysomnographic data (Day 0)				
AHI (/h)		37.6 ± 6.6		37.9 ± 5.1
RERA (/h)		47.2 ± 12.6		42.3 ± 14.1
RDI (/h)		84.8 ± 12.1		80.2 ± 13.2
Arousal index (/h)		57.1 ± 16.9		56.3 ± 12.0
Apnea index (/h)		19.5 ± 11.1		18.4 ± 7.5
Lowest SpO_2 (%)		84.9 ± 4.5		83.7 ± 4.1
CPAP parameters	**Day 90**		**Day 180**	
AHI (/h)	6.7 ± 1.0***		4.6 ± 0.3$^{\dagger\dagger\dagger,\#}$	N/A
CPAP usage index (%)	81.4 ± 9.6		86.0 ± 6.0	N/A
CPAP average daily use (h)	6.9 ± 0.7		7.0 ± 0.5	N/A
CPAP average pressure (cm H_2O)	13.2 ± 2.3		13.2 ± 1.6	N/A
CPAP lower pressure (cm H_2O)	8.8 ± 1.0		10.8 ± 0.8	N/A
CPAP upper pressure (cm H_2O)	17.4 ± 2.0		17.4 ± 1.3	N/A

Data are expressed as mean ± SD. CPAP: continuous positive airway pressure, AHI: apnea hypopnea index, RERA: respiratory effort related arousals, RDI: respiratory disturbance index, N/A: not assessment. ***, $p < 0.01$ visit 1 vs. visit 2, $^{\dagger\#}$ $p < 0.001$ visit 1 vs. visit 3, $^{\#}$ $p < 0.05$ visit 2 vs. visit 3 in CPAP group

shown in Table 2. There were no significant differences between CPAP and non-CPAP groups in any sleep stage parameters studied, including sleep efficiency, non-rapid eye movement (stage 1, 2, 3), and rapid eye movement. AHI, RERA, RDI, arousal index, apnea index, and lowest SpO_2 of subjects in the CPAP group did not differ from those in the non-CPAP treatment group. The average CPAP usage index for Day 180 was 86.0 ± 6.0%. The average nightly use of approximately seven hours per night indicates adequate CPAP use. The average CPAP pressure was 13.2 ± 1.6 cmH_2O. AHI as measured by the CPAP device gradually decreased over time following CPAP treatment ($p < 0.001$) but no changes in other CPAP parameters were observed.

Association between sleep severity and inflammation and oxidative stress in OSA patients are shown in Table 3 show positive correlations between AHI and MDA levels ($r = 0.4728$, $p < 0.01$), ALT levels ($r = 0.6081$, $p < 0.001$), AST ($r = 0.6299$, $p < 0.001$), NLR ($r = 0.3943$, $p < 0.05$), PLR ($r = 0.3319$, $p < 0.05$), and hs-CRP levels ($r = 0.5728$, $p < 0.001$). An arousal index was positively correlated with MDA levels ($r = 0.4275$, $p < 0.01$), ALT levels ($r = 0.7417$, $p < 0.001$), AST levels ($r = 0.6850$, $p < 0.001$), PLR ($r = 0.3502$, $p < 0.05$), and hs-CRP levels ($r = 0.5966$, $p < 0.001$). Apnea index was positively correlated with MDA levels ($r = 0.3660$, $p < 0.01$), ALT levels ($r = 0.7674$, $p < 0.001$), AST levels ($r = 0.6662$, $p < 0.001$), PLR ($r = 0.3344$, $p < 0.05$), and hs-CRP levels ($r = 0.5650$, $p < 0.001$). SpO_2 was negatively correlated with ALT levels ($r = -0.4840$, $p < 0.001$), AST levels ($r = -0.4539$, $p < 0.01$) and hs-CRP levels ($r = -0.4799$, $p < 0.001$).

In regard to oxidative stress, improvement in MDA after 90 and 180 consecutive days of CPAP treatment was observed ($p < 0.001$). Such improvement was not found in the non-CPAP group (Table 4). There was no significant change in BMI in either group. Liver inflammation parameters following CPAP treatment are shown in Table 4. In the CPAP treatment group, subjects showed decreased ALT levels ($p < 0.05$) on Day 90 and 180 compared to Day 0, while the non-CPAP group showed significant increases in ALT levels ($p < 0.05$) on Day 90, ($p < 0.001$) on Day 180 compared to Day 0, and ($p < 0.05$) Day 180 compared to Day 90 (Table 4). Systemic inflammation parameters in OSA patients, the subgroups CPAP, and non-CPAP treatment groups are shown in Table 4. On Day 90, NLR, PLR, and hs-CRP levels were lower in CPAP group compared to Day 0 ($p < 0.01$, $p < 0.05$, and $p < 0.01$, respectively). Interestingly, NLR, PLR, and hs-CRP levels decreased further after 180 days of CPAP treatment ($p < 0.001$) compared to Day 0. There were no differences in NLR, PLR, and hs-CRP levels between Day 0 and Day 90 in the non-CPAP group.

Table 3. Association between liver and systemic inflammation and oxidative stress and sleep severity in OSA patients

	OSA patients	Correlation coefficient			
	(n=40)	AHI	Arousal index	Apnea index	Lowest SpO_2
Oxidative stress parameters					
MDA (μmol/L) Normal:1.4 - 2.4 (μmol/L) (Tichanon et al., 2016)	14.5 ±4.0	0.4728**	0.4275**	0.3660*	-0.1031
Liver inflammation parameters					
ALT (U/L) Normal:7-56 (U/L) (Gowda et al., 2009)	22.5 ± 14.1	0.6081***	0.7417***	0.7674***	-0.4840***
AST (U/L) Normal:< 35 (U/L) (Gowda et al., 2009)	22.2 ± 9.2	0.6299***	0.6850***	0.6662***	-0.4539**
Systemic inflammation parameters					
NLR Normal:2.7 ± 1.5 (NI, 2016)	2.1 ±0.6	0.3943*	0.3032	0.2228	-0.0635
PLR Normal:113.0 ± 32.0 (NI, 2016)	134.2 ±8.3	0.3319*	0.3502*	0.3344*	-0.0813
hs-CRP (mg/dl) Normal:< 1 (mg/dl) (Kim et al., 2016)	3.0 ±2.2	0.5728**	0.5966***	0.5650***	-0.4799**

Data are expressed as mean ± SD. MDA: malondialdehyde, AHI: apnea hypopnea index, ALT: alanine aminotransferase, AST: aspartate aminotransferase, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, hs-CRP: high sensitivity C-reactive protein.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ significant levels of liver, systemic inflammation and oxidative stress vs. sleep parameters.

Table 4. Liver and systemic inflammation and oxidative stress in OSA patients (CPAP and non-CPAP treatment groups)

	CPAP (n=20)			Non-CPAP (n=20)		
	Day 0	Day 90	Day 180	Day 0	Day 90	Day 180
Oxidative stress parameters						
MDA (μmol/L)	14.7 ±3.5	10.0 ±2.6***	6.2 ±2.3$^{\#\#\#,\downarrow\downarrow}$	14.3 ±4.6	14.1 ±4.3	16.0 ±4.2
Liver inflammation parameters						
ALT (U/L)	24.7 ±16.4	19.9 ±8.1*	19.4 ±7.4$^{\#}$	20.3 ±11.4	23.5 ±8.8§	26.7 ±7.9$^{\gamma\gamma\gamma,\beta}$
AST (U/L)	23.0±10.6	19.6 ±7.5*	16.9 ±5.6$^{\#\#\#}$	21.4 ±7.8	24.7 ±6.4§	25.2±5.6$^{\gamma}$
Systemic inflammation parameters						
NLR	2.1 ±0.6	1.7 ±0.4**	1.5 ±0.3$^{\#\#\#}$	2.0 ±0.6	2.3 ±0.5	2.5 ±0.4$^{\gamma}$
PLR	135.8 ±10.1	121.7 ±19.7*	111.8±23.7$^{\#\#\#}$	132.6 ±5.9	148.9 ±33.1	168.3 ±36.3$^{\gamma\gamma}$
hs-CRP (mg/dl)	3.2 ±2.3	2.3 ±1.5**	2.1 ±1.3$^{\#\#\#}$	2.9 ±2.1	3.3 ±1.8	3.7 ±1.7$^{\gamma\gamma}$

Data are expressed as mean ± SD. MDA: malondialdehyde, CPAP: continuous positive airway pressure, ALT: alanine aminotransferase, AST: aspartate aminotransferase, NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, hs-CRP: high sensitivity C-reactive protein. * p < 0.05, ** p < 0.01, *** p < 0.001 Day 0 vs. 90, $^{\#}$ p < 0.05, $^{\#\#}$ p < 0.01, $^{\#\#\#}$ p < 0.001 Day 0 vs. 180, $^{\downarrow\downarrow}$ p <0.001 Day 90 vs. 180 in CPAP group. § p < 0.05 Day 0 vs. 90, $^{\gamma}$ p < 0.05, $^{\gamma\gamma}$ p < 0.01, $^{\gamma\gamma\gamma}$ p < 0.001 Day 0 vs. 180, $^{\beta}$p <0.05 Day 90 vs. 180 in non-CPAP group.

However, NLR ($p < 0.05$), PLR ($p < 0.01$), and hs-CRP levels ($p < 0.01$) on Day 180 significantly increased compared to Day 0 (Table 4).

DISCUSSION

The main findings of this study were that (i) apnea severity was associated with oxidative stress and inflammation parameters in severe OSA patients; (ii) after CPAP therapy characterized by 86 ± 6% of CPAP usage index and 7.0 ± 0.5 h/night for 180 days, significant improvements in MDA, ALT, NLR, PLR, and hs-CRP levels were observed, whereas these parameters worsened in the non-CPAP group after 180 days.

We observed a correlation between sleep apnea severity with MDA levels in severe OSA patients, which is in agreement with previous studies in moderate to severe OSA patients (Celec et al., 2012; Wang et al., 2010). Nevertheless, there was only one study reporting no change in MDA levels with apnea severity in moderate OSA patients (Yamauchi et al., 2005). This discrepancy could be due to the later study being done in only moderate OSA patients whereas the two former studies and our study were conducted in moderate to severe and severe OSA patients, respectively. The correlation between sleep apnea severity indices with oxidative stress levels may be due to hypoxia reoxygenation injury enhancing the release of free radicals, which subsequently leads to injury of cells resulting in increased lipid peroxidation (MDA) (Asker et al., 2015). The present study using CPAP seven hours per night for three months decreased MDA levels and even more for six months compared to pre-CPAP therapy. This finding is comparable to the majority of other studies that suggest that using CPAP for four hours or more per night significantly reduces MDA levels after three months (Celec et al., 2012; Hernandez et al., 2006; Tichanon et al., 2016). This study is the first study demonstrating a further decrease in MDA levels following six months of CPAP treatment. CPAP is effective in suppressing OSA-associated chronic intermittent hypoxia, which triggers oxidative stress (Tichanon et al., 2016). The use of CPAP in OSA patients resulted in decreased oxidative stress and reduction or elimination of hypoxia. This study found no significant increases in MDA levels after three and six months in non-CPAP patients compared to Day 0. Unfortunately, there have been no studies following up on MDA levels in non-CPAP patients. It is probable that IH found in non-CPAP group was not severe enough to increase MDA levels. Longitudinal research is crucial to evaluate whether MDA levels increase if OSA patients are left untreated.

We observed a significantly positive correlation between apnea severity and ALT. This observation is in lines with previous studies that showed the association between liver enzyme levels and sleep apnea parameters

(Aron-Wisnewsky et al., 2016; Cakmak et al., 2015). However, other studies found no correlations between sleep apnea severity with liver function (Daltro et al., 2010; Kallwitz et al., 2007). This disagreement is probably due to severity of OSA patients recruited to each study. The positive correlation between liver enzyme levels and indices of sleep apnea severity observed in OSA patients indicates that as the severity of sleep apnea increases, there is a concomitant increase in ischemia reperfusion inducing oxidative stress and inflammation in hepatocytes cells (Cakmak et al., 2015). Our study showed a significant decrease in ALT levels after CPAP treatment of seven hour per day for three and six consecutive months, which is in agreement with the majority of previous studies (Shpirer et al., 2010; Toyama et al., 2014). This observation could be due to CPAP use reducing multiple cycles of hypoxia reoxygenation. Moreover, CPAP therapy prevents the pathogenesis of NAFLD in OSA patients by reducing fat accumulation, insulin resistance, and liver inflammation (Jouët et al., 2007).

In the present study, we found that sleep apnea severity indices were positively correlated with systemic inflammation (NLR, PLR, and hs-CRP). This discrepancy is probably due to differences in the severity of OSA patients participated in each study. Some previous studies were done in mild to moderate OSA patients only (Kim et al., 2016; Koseoglu et al., 2015), while the present study and other studies were conducted in severe or moderate to severe OSA patients (Ryan, Taylor, & McNicholas, 2009). This correlation may also reflect a systemic inflammatory response to hypoxemia, which is known to trigger activation of neutrophils, platelet, IL-6, and hs-CRP (Calvin et al., 2009; Kim et al., 2016; Kivanc & Kulaksizoglu, 2017). These neutrophils and platelets in turn interact with the pro-inflammatory cytokines resulting in increases in NLR and PLR in patients with severe OSA (Kivanc & Kulaksizoglu, 2017). Nocturnal hypoxemia and sleep disturbances result in increases in IL-6 and hs-CRP (Kim et al., 2016; Shamsuzzaman et al., 2002). Another noteworthy observation made in our study was the decrease in NLR, PLR, and hs-CRP after CPAP therapy, which is consistent with previous observations (Koseoglu et al., 2015; Ryan, Taylor, & McNicholas, 2009; Shamsuzzaman et al., 2002). CPAP therapy ameliorates repetitive hypoxia and reoxygenation, which plays an important role in regulating an inflammatory response among patients with OSA (Calvin et al., 2009). The use of CPAP in OSA patients resulted in decreased systemic inflammation levels.

CONCLUSIONS

In summary, our study demonstrates that severity of OSA was correlated with oxidative stress and inflammation. The present study found clinical benefits of adequate CPAP use (usage index of 86 ± 6% and 7.0 ± 0.5 h/night for six consecutive months) in treating severe OSA patients, as evidenced by improved oxidative stress, and inflammation.

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