THE INFLAMMATION IN OBSTRUCTIVE SLEEP APNEA SYNDROME

OBSTRUKTİF UYKU APNE SENDROMU'NDA İNFLAMASYON

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Key words: Obstructive Sleep Apnea Syndrome, Inflammation, Obesity, Insulin Resistance.

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ÖZET

Amaç: *Obstruktif uyku apne sendromu (OUAS) ve inflamasyon arasındaki ilişki tartışmalıdır. Uyku apne ve obesite farklı mekanizmalarla inflamasyonu arttırabilir. Bu çalışma uyku apnesi ve obesite ile proinflamatuar durumun ilişkisini inceledi.*

Metod: *Toplam 133 olguya polisomnografi yapıldı. Polisomnografileri yapılarak, apne hipopne indeksi (AHI)>5 olan 112 OUAS tanılı hasta ve AHI<5 olan 21 kontrol grubu birey çalışmaya dahil edildi. Kontrol grubu bireyler grup A olarak kabul edildi. Bununla birlikte OUAS tanılı hastalar VKİ'lerine göre non-obese grup (B grup) (VKİ<30) ve obese grup (C grup) (VKİ>30) olarak iki gruba ayrıldı.*

Bulgular: *Tüm inflamatuar sitokinler (CRP, hs CRP, TNF-á, IL-6) obez uyku apneli hastalarda kontrol grubu bireylerden anlamlı olarak daha yüksekti. İnsülin rezistansı obez uyku apneli hastalarda obez olmayan hastalardan ve kontrol grubundan daha yüksekti fakat insülin rezistansı kontrol grubu ve obez olmayan uyku apneli hastalar arasında farklı değildi. Tüm inflamatuar sitokinler pearson korelasyon analizinde VKİ ile anlamlı ilişki gösterdi. Ancak multiple varians analizinde CRP, hs CRP VKİ ile anlamlı ilişkiliyken, TNF-á, IL-6'nın VKİ ile anlamlı ilişkisi yoktu. Tüm inflamatuar sitokinler yine bu analize göre desaturasyon indeksi ile anlamlı ilişkiliydi.*

SUMMARY

Aim: *The association between obstructive sleep apnea syndrome (OSAS) and inflammation remains controversial. This study investigated the relationship between OSAS and obesity with pro-inflammatory state.*

Method: *A total of 133 consecutive subjects who were referred for polysomnography. 112 were documented to have OSAS defined as AHI >5 and 21 control subjects with AHI <5 were selected upon polysomnography. Control group has been accepted as A group. In addition, patients with OSAS were divided into the following two groups based on the BMI as non-obese (B group) (BMI <30) and obese (C group) (BMI>30).*

Result: *CRP, hs CRP, TNF-á, IL-6 were significantly higher in the obese patients with OSAS than in the control group. Insulin resistance was higher in obese patients with sleep apnea than both in non-obese patients and control group but insulin resistance did not differ between control group and non-obese patients with sleep apnea. All of inflammatory cytokines showed significant associations with BMI in pearson correlation analysis. However, in multiple variance analysis, CRP, hs CRP were significant associated with BMI while TNF-á, IL-6 were not significant associated BMI. All of inflamatory cytokines were significantly associated with desaturation index according to this analysis.*

Sonuç: *Adipöz dokunun proinflamatuar durumun gelişiminde anahtar rol oynadığı için bu hastalarda obesite hem uyku apnesinin şiddetini arttırır hem de inflamasyonun artışını tetikler. OSAS'ın ve metabolik bozuklukların erken tespiti kardiovasküler morbidite ve mortalitenin azalmasına yardımcı olur.*

Conclusion: *Obesity increases both severity of sleep apnea and causes aggravate of inflammation in these patients because adipose tissue play a key role for the development of the proinflammatory state. Early detection of OSAS and metabolic dysfunction may help to decrease the cardiovascular morbidity and mortality.*

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive upper airway closure during sleep resulting in repeated reversible blood oxygen desaturation and fragmented sleep (1). OSAS is a serious, prevalent condition that has significant mortality and morbidity when untreated (2). Accumulating evidence suggests that OSAS is associated with alterations in glucose metabolism, insulin resistance and inflammation. Although the pathophysiology of metabolic dysfunction in OSAS is not well understood, there are several biologically likely pathways to explain this, including the effects of sleep deprivation and intermittent hypoxia (3). Studies of murine models indicate that intermittent hypoxemia for development metabolic dysfunction has an important contribution (4). Sleep disordered breathing increases incidence of cardiovascular morbidity by hormonal changes and metabolic disorders (5). Abnormalities in lipid metabolism that occur in response to chronic intermittent hypoxia in patients with sleep-disordered breathing may increase the cardiovascular risk in an already susceptible population (6).

Excess weight in adults is clearly associated with increased incidence of type-2 diabetes and impaired glucose tolerance (7). Obesity is very common in patients with OSAS. Sleep disordered breathing is a complication of obesity estimated to occur in about 4-6% of overweight individuals (5). The results of sleep apnea and obesity are similar to each other, such as increased cardiovascular disease and increased mortality rates. While obesity is the primary risk factor for the development of systemic inflammation and sleep apnea (8), sleep apnea may increase the inflammatory and metabolic disorders (9). Nevertheless, it is not known whether concomitant OSAS is implicated in metabolic dysregulation and systemic inflammation in severe obesity. The strong relation between these two disorders appears to be complex, so it is crucial to examine it in order to understand the disordered breathing pathophysiology. The associations between sleep apnea with inflammation and obesity remains controversial and there are different results about these relations in studies. This study investigated the relationship between sleep-disordered breathing with insulin resistance and pro-inflammatory state. In addition we also examined the relationship between obesity and these abnormalities.

METHOD

Subjects

Consecutive subjects admitted to the Sleep Laboratory at the Faculty of Medicine, Department of Pulmonary Medicine, Hospital, because of a clinical referral for suspected sleep apnea were recruited. Exclusion criteria were subjects with known diabetes mellitus (DM) on medications, acromegaly, chronic renal failure, on systemic steroid treatment, and on hormonal replacement therapy. A questionnaire on demographics, sleep symptoms, medical history, and medications were completed. Body mass index (BMI) (kg/m2) was calculated by measuring weight and height. Pulmonary function tests (PFT) were performed with flow sensitive spirometer. Fasting venous blood samples were taken from all subjects. Venous blood was then obtained for the measurement of inflammatory cytokines (CRP, hs CRP, IL-6, TNF-á) and glucose and insulin. Extracted

serum was stored at 70°C for further analyses. Insulin resistance method by homeostasis assessment model (HOMA-IR) was analyzed in venous blood. The HOMA-IR was used to calculate insulin resistance according to the following. formula: HOMA-IR: fasting plasma insulin (mU/mL) x fasting plasma glucose (mg/dL)/22.5 (10). Subjective sleepiness of all subjects was assessed using the Epword Sleepiness Scale (ESS).

Total of 133 consecutive subjects who were referred for polysomnography and 112 (male/female: 85/27) were documented to have OSAS defined as an apnea–hypopnea index (AHI) >5. Twenty one control subjects (male/female:16/5) with an AHI <5 were selected upon polysomnography. None of the patients and the controls have used nasal CPAP-BPAP due to OSAS. Control group has been accepted as a A group (group A, n:21). The patients with OSAS were divided into the following two groups based on the BMI: patients with BMI<30 (group B, n:49), patients with BMI >30 (group C, n:63). All subjects gave written informed consent to taking. The study was approved by the local ethics committee.

Polysomnography

Standard nocturnal polysomnography was performed with recording of sleep stages (electroencephalography, chin muscles electromyography, electro-oculography), measurements of oronasal airflow, snoring, respiratory movements and oxygen saturation (Sa,O2) with a finger pulse oximeter (sleep screen). Sleep stages were scored using standard criteria. Apnea was defined as cessation of airflow for 10 s. Hypopnea was defined as a 30% reduction of airflow or respiratory movements accompanied by a 3% decrease in Sa,O2 and/or followed by an arousal. Using this definition for hypopnea, the threshold of apnea and hypopnea per hour of sleep was chosen to define OSAS. Subjects with an apnea/hypopnea index (AHI) of <5 were classified as nonapneic snorings (11).

Epword Sleepiness Scale

The Epword Sleepiness Scale (ESS) is simple, eight item self-administered scale wich is widely used in clinical practice to quantify the level of daytime sleepiness in situations of different soporificity. I has a total score range of 0-24 and scores>10 are indicative af high level of daytime sleepiness (12).

Statistical analysis

All clinical parameters were summarised by descriptive statistics and expressed as mean ± SD. Analysis of anova (dunnett's T3) was used to compare age, sex, BMI, severity of sleep apnea, inflammatory cytokines in three groups (control group, non-obese patients with sleep apnea, obese patients with sleep apnea). The relation between all of inflammatory cytokines and BMI, AHI, DI, HI, AI was investigated by using pearson correlation analysis in all subjects. In addition, relationships between with CRP, hsCRP, IL-6, TNF-ά and sex, age, BMI, AHI, DI, AI, HI were ascertained using multivariable linear regression in all subjects.

RESULTS

During the study period, 112 consecutive patients with OSAS and 21 nonapneic snores were referred to the sleep laboratory. Table 1 summarizes the study characteristics of the 133 subjects. Mean age, sex were not differ all groups. BMI was significantly higher in the obese patients with sleep apnea than in the control group and non-obese patients with sleep apnea. However BMI of control group and non-obese patients with sleep apnea was similar. CRP, hsCRP, IL-6, TNF-ά values did not differ between non-obese patients with sleep apnea and control group. CRP, hsCRP, IL-6, TNF-ά values did not differ between non-obese and obese patients with sleep apnea too. However, CRP, hsCRP, IL-6 values were significantly higher in the obese patients with sleep apnea than in the control group but TNF-ά value borderline higher in the obese

patients with sleep apnea than in the control group. AHI, ESS, DI were higher in obese and non-obese patients with sleep apnea than in the control group. In addition, AHI was higher in obese patients with sleep apnea than in non-obese patients with sleep apnea. Insulin resistance was higher in obese patients with sleep apnea than both in non-obese patients and control group but insulin resistance did not differ between control group and non-obese patients with sleep apnea (Table 1).

The relation between all of inflammatory cytokines with BMI, AHI, DI, AI, HI was examined in all subjects according to the pearson correlation analyses. There were found positive relation between BMI and CRP (p: 0.0001), hs CRP (p: 0.0001), IL-6 (p: 0.01), TNF-ά. (p: 0.02). DI was significant associated with all of inflammatory cytokines (CRP (p: 0.0001), hs CRP (p: 0.002), IL-6 (p: 0.007), TNF-ά. (p: 0.02)). AHI was significant associated with CRP (p: 0.02), IL-6 (p: 0.003), TNF-ά. (p: 0.01). While HI was significant associated with CRP (p: 0.0001), hs CRP (p: 0.0001), AI was significant associated with IL-6 (p: 0.002), TNF-ά. (p: 0.004) (Table 2).

Table 1. Clinical Features, Values of Inflammatory Cytokines and HOMA-IR of Nonobese and Obese Patients with Obstructive Sleep Apnea and Control Group

	A group: Control n:21 Mean ± SD	B group: NOB OSA n:49 Mean± SD	p value *	C group: OB OSA n:63 Mean± SD	p value #	p value ±
Age	5.1 ± 9.3	45.7± 10.8	0.9	50.0 ± 9.2	0.1	0.08
Sex male/ female	16/5	42/7	0.9	43/20	0.1	0.08
CRP	0.2 ± 0.1	0.3 ± 0.3	0.1	0.4 ± 0.3	0.001	0.2
hsCRP	3.1 ± 2.1	4.9 ± 3.6	0.4	5.9 ± 3.5	0.0001	0.4
IL-6	5.5 ± 4.1	9.9 ± 18.9	0.3	18.0 ± 28.0	0.003	0.2
TNF-ά	9.4 ± 3.1	10.7 ± 4.1	0.4	13.9 ± 13.5	0.05	0.2
IR	2.7 ± 1.3	2.5 ± 1.4	0.8	3.9 ± 2.2	0.02	0.0001
BMI	28.7 ± 4.2	27.0 ± 1.7	0.2	33.8 ± 3.8	0.0001	0.0001
ESS	6.0 ± 2.6	9.5± 5.6	0.004	11.0 ± 5.4	0.0001	0.3
AHI	2.5 ± 1.6	32.6 ± 22.8	0.0001	43.5 ± 28.8	0.0001	0.03
DI	4.8 ± 4.5	3.1 ± 26.6	0.0001	31.4 ± 26.7	0.0001	0.2

Statistical significance p<0.05
**:p values <0.05 (when comparison of control group and non-obese patients with sleep apnea)*
 # :p values <0.05 (when comparison of control group and obese patients with sleep apnea)
± :p values <0.05 (when comparison of obese and non-obese patients with sleep apnea)
SD: Standart Deviation
NOB: Non-obese
OB: Obese
AHI: Apnea hypopnea index
BMI:Body mass index
ESS: Epworth sleepness scala
DI: Desaturation index

We examined the association with CRP, hs CRP, IL-6, TNF-ά and age, sex, AHI, BMI in all subjects according to the multiple linear regression analysis. CRP, hs CRP values did not show significant associations with AHI but showed significant associations with BMI (p: 0.0001, p: 0.002, respectively).On the other hand, IL-6, TNF-ά values showed significant associations with AHI (p: 0.004, p: 0.01, respectively) but did not show significant associations with BMI (Table 3). The relation between CRP, hs CRP, IL-6, TNF-alfa and age, sex, DI, BMI was examined in all subjects according to the multiple linear regression analysis. All of inflammatory cytokines (CRP, hs CRP, IL-6, TNF-ά) were significant associated with DI (p: 0.004, p: 0.01, p: 0.007, p: 0.02, respectively). CRP, hs CRP values were associated with BMI (p: 0.0001, p: 0.01, respectively) but IL-6, TNF-ά values were not associated with BMI (table 4). The relation between CRP, hs CRP and age, sex, HI, BMI was examined in all subjects according to this analysis. CRP, hs CRP values were significant associated both HI (p: 0.004, p: 0.002, respectively) and BMI (p: 0.0001, p: 0.005, respectively) (Table 5). In addition, the relation between IL-6, TNF-ά and age, sex, AI, BMI was examined in all subjects according to this analysis. IL-6, TNF-ά values were significant associated AI (p: 0.002, p: 0.004, respectively) but and were not associated BMI (Table 6).

Table 2. The association between BMI, AHI, DI, HI, AI and all of inflamatuary cytokines in all subjects according to pearson correlation

	CRP		hsCRP		IL-6		TNF-ά	
	r	p	r	p	r	p	r	p
BMI	0.40	0.0001	0.30	0.0001	0.22	0.01	0.20	0.02
AHI	0.20	0.02	0.16	0.05	0.25	0.003	0.22	0.01
DI	0.32	0.0001	0.26	0.002	0.23	0.007	0.20	0.02
HI	0.34	0.0001	0.36	0.0001	0.00	0.9	-0.03	0.6
AI	0.13	0.1	0.08	0.3	0.27	0.002	0.25	0.004

Statistical significance p<0.05
BMI:Body mass index
AHI: Apnea hypopnea index
DI: Desaturation index
HI:Hipopne index
AI:Apne index

Table 3. The Predictors of CRP, hs CRP, IL-6, TNF-alfa in all subjects

	CRP			hsCRP			IL-6			TNF-ά		
	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
			14 %			13 %			06 %			04 %
Sex	0.006	0.9		0.06	0.7		-0.04	0.5		-0.008	0.9	
Age	0.13	0.1		0.20	0.01		-0.02	0.7		-0.05	0.5	
AHI	0.10	0.2		0.08	0.3		0.25	0.004		0.22	0.01	
BMI	0.38	0.0001		0.26	0.002		0.13	0.1		0.12	0.1	

Statistical significance p<0.05
AHI: Apnea hypopnea index
BMI:Body mass index

Table 4. The Predictors of CRP, hs CRP, IL-6, TNF-alfa in all subjects

	CRP			hsCRP			IL-6			TNF-ά		
	β	p	R^2	β	p	R^2	β	p	R^2	β	p	R^2
			20 %			16 %			05 %			04 %
Sex	-0.07	0.3		- 0.006	0.9		-0.04	0.5		-0.007	0.9	
Age	0.12	0.1		0.20	0.01		-0.02	0.8		-0.05	0.5	
DI	0.24	0.004		0.20	0.01		0.23	0.007		0.20	0.02	
BMI	0.32	0.0001		0.21	0.01		0.14	0.09		0.13	0.1	

Statistical significance p<0.05
BMI: Body mass index
DI: Desaturation index

Table 5. The Predictors of CRP, hs CRP in all subjects

	CRP			hsCRP		
	β	p	R^2	β	p	R^2
Intercept			23%			23%
Sex	0.01	0.8		0.05	0.5	
Age	0.09	0.2		0.18	0.03	
HI	0.25	0.004		0.27	0.002	
BMI	0.34	0.0001		0.25	0.005	

Statistical significance p<0.05
BMI: Body mass index
HI: Hipopne index

Table 6. The Predictors of IL-6, TNF-alfa in all subjects

	IL-6			TNF-ά		
	β	p	R^2	β	p	R^2
Intercept			07%			06%
Sex	-0.06	0.4		-0.02	0.7	
Age	-0.01	0.8		-0.05	0.5	
AI	0.27	0.002		0.25	0.004	
BMI	0.14	0.09		0.13	0.1	

Statistical significance p<0.05
AI: Arousal index
BMI:Body mass index

DISCUSSION

AHI in obese patients with sleep apnea was significant higher than non-obese with sleep apnea. All of inflammatory cytokines in obese patients with sleep apnea were higher than in control group while this difference was not showed between non-obese patients and control group. Insulin resistance was also higher in obese patients with sleep apnea than both in non-obese patients and control group but insulin resistance did not differ between control group and non-obese patients with sleep apnea. In simple pearson analyses, CRP, IL-6, TNF-ά were associated with AHI and all of inflammatory cytokines were associated with DI. On the other hand, CRP, hs CRP were associated with HI, while IL-6, TNF-ά were associated with AI. BMI showed significant

association with all of inflammatory cytokines according simple pearson corelation analyses but BMI was associated with only CRP and hsCRP values according to multiple regresion analyses when sex and age taken into account. Accordingly, it may be considered that the both intermittan hypoxia and obesity in patients with sleep apnea may cause increase inflammation. Obesity both may increase severity of sleep apnea and the augmentation of inflammatory cytokines.

Previous studies have used different methodological approaches and different populations, and results have been conflicting. The important findings have emerged from several other clinic-based studies on the association between sleep-disordered breathing and inflammatory cytokine. The study by Vgontzas et al indicated that sleep apnea in obese middle-aged men is associated with inflammatory cytokine elevations (TNF-ά and IL-6). They concluded that the independent effects of these disturbances could be explained by microawakening-and/or hypoxia-related nocturnal increases in sympathetic system and hypothalamic-pituitary-adrenal axis activities (13). Similarly, the results of a cross-sectional study demonstrated that cyclical hypoxia could lead to metabolic disorders by promoting the release of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, indicating that indices of sleep-related hypoxemia are related to metabolic dysfunction (14). Another study demonstrated that inflammatory parameters such as hs-CRP increase with OSAS severity (15). On the other hand, McArdle et al did not find relationship between OSAS with increased levels of TNF-ά (16). In study of Kono et al, the percentage of patients presenting at least two metabolic abnormalities (among hypertension, dyslipidemia, and hyperglycemia) was significantly higher in the OSAS group than in the non-OSAS group matched for age, BMI (17). The Study in middle-aged and overweight men revealed that increasing AHI and the severity of oxygen desaturation was associated with worsening insulin resistance independent of obesity in mildly obese (18). However, the different results in studies on the relationship between insulin resistance with OSAS have been reported. On the other hand other the study showed that the relationship between insulin resistance and sleep-disordered breathing was entirely dependent on body mass (19). Again, Gruber et all determined that OSAS is independently associated with the metabolic syndrome but not insulin resistance state (20). Similar to our study, Ip et al showed that obesity was the major determinant of insulin resistance but sleep disordered breathing parameters (AHI and minimum oxygen saturation) were also independent determinants of insulin resistance with multiple linear regression analysis (21).

The data presented in here indicate that indices of sleep-related hypoxemia and obesity are related to inflammation independently each other. Similarly, our study showed that both intermittan hypoxia and obesity increase inflammatory cytokines. It can be considered that obesity corresponds to a sub-clinical inflammatory condition that promotes the production of pro-inflammatory cytokines (22). Obesity with enlarged adipose cells leads to a marked increase in the expression of pro-inflammatory cytokines in the adipose tissue while expression of the antiinflammatory adipokine, adiponectin is reduced (23). Sheu and et investigated whether weight loss can lead to improvement of the proinflammatory state in nondiabetic obese women. Their study showed that hsCRP, TNF-α decreased significantly after by 5% of initial weight loss in this population (24).

A study in otherwise lean, healthy mice indicated that intermittent hypoxia can cause acute insulin resistance independent of autonomic activity (25). Study in healthy volunteers indicated that short-term episodic hypoxia during the daytime alters glucose disposal by decreasing insulin sensitivity and glucose effectiveness. Intermittent hypoxia was also associated with a shift in sympathovagal balance toward an increase in sympathetic nervous system activity. Thus they speculated that intermittent hypoxemia is a central mechanism responsible for metabolic

dysfunction in patients with OSAS and that the sympathetic nervous system is a putative mediator (26). In addition studies concerning effects of treatment on the association between sleep-disordered breathing and insulin resistance were suggestive and significant. Brooks et al indicated that treatment of OSAS by CPAP in obese noninsulin-dependent diabetic patients may improve insulin responsiveness (27). The study in a group of very obese subjects with type 2 DM demonstrated that effective treatment of sleep-disordered breathing (ie, the CPAP pressure that best eliminated SDB) led to improved glycemic control, as assessed by HbA1c improvement in compliant CPAP users (2).

In conclusion, these remarkable associations raise the possibility that sleep apnea and accom for panying obesity may be a important risk factor inflammation. Obesity increases both severity of sleep apnea and causes aggravate of insulin resistance and inflammation in these patients because adipose tissue play a key role for the development of the proinflammatory state. It appears that there is a continuum of these abnormalities in sleep apnea and obesity, with its most severe form in obese people with sleep apnea. The presence of obesity may be a useful clinical indicator of the presence of metabolic abnormalities in OSAS. Approaches for the treatment of obesity may be useful for prevention of metabolic disorders in these patients. Early detection of OSAS and metabolic dysfunction may help to decrease the cardiovascular morbidity and mortality.

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