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The relationship between nasal mucociliary clearance time and the degree of smoking dependence in smokers with obstructive sleep apnea syndrome

Abstract

Introduction: The aim of this study was to investigate the relationship between nasal mucociliary clearance time (NMCT), degree of smoking dependence, cumulative smoking burden and OSAS severity in smokers.

Material and methods: 123 patients (Group 1) with OSAS and 92 healthy controls (Group 2) were included in the study. Group 1 was divided into smokers (Group 1a) and non-smokers (Group 1b). In Group 1a, cumulative smoking burden and Fagerström nicotine dependence test (FNCT) were questioned. Saccharin test was applied to Groups 1 and 2. Student-t, Mann-Whitney-U, Anova, Kruskal-Wallis tests were used to compare the means.

Results: NMCT was higher in Group 1 than Group 2 ($p = 0.005$). The duration of NMCT was higher in Group 1A than Group 1B ($p = 0.002$). In Group 1a, NMCT values of mild and moderate OSAS patients were longer than in Group 1b ($p = 0.02$, $p = 0.01$, respectively). NMCT values of patients with mild dependence were shorter than those with moderate or severe dependence ($p = 0.032$, $p < 0.001$, respectively).

Conclusion: Mucociliary clearance time was higher in smokers with OSAS than non-smokers. While OSAS has a negative effect on mucociliary clearance, smoking also exacerbates the condition.

Key words: smoking, obstructive sleep apnea, nasal mucociliary clearance time, saccharine test

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Introduction

Mucociliary clearance is the most important mechanism in the protection of upper and lower airways against pathogens, foreign bodies and toxins [1]. Therefore, an effective nasal mucociliary clearance (NMC) depends on the relationship between epithelial structure integrity, ciliary stroke frequency and mucus quantity and quality [2, 3]. Disorders in these defence mechanisms are effective in the pathogenesis of the inflammation and obstruction of small airways, increased susceptibility to respiratory tract infections, lung damage, tissue repair problems and progression of chronic respiratory diseases [4].

For the evaluation of nasal mucociliary clearance, an *in vivo* technique of saccharin clearance was described by Andersen *et al.* [5] in 1974 and was modified by Rutland and Cole [6]. The mean period of clearance varies between 7 and 15 minutes, and transport time longer than 30 minutes indicates that nasal mucociliary clearance is impaired. Simple, effective and reproducible are important for clinical ease of use [5–7].

Obstructive sleep apnea syndrome (OSAS) is a sleep-related respiratory distress disorder [7] that, despite an ongoing effort to breathe, causes airflow reduction or complete cessation of relaxation of the pharyngeal muscles and narrowing or obstruction of the upper airways [8]. The preva-

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lence of OSAS is 13–33% in middle-aged men and 6–19% in women. It is thought that the prevalence will continue to increase due to the obesity epidemic in middle and high income countries [9]. OSAS disrupts the quality of life with excessive daytime sleepiness. Because of increasing cardiovascular morbidity and mortality, it is very important in terms of quality of life [10, 11].

Smoking habits and the number of cigarettes smoked per day are reported to be associated with impairment of nasal mucociliary clearance time (NMCT) [12]. Smoking was also associated with OSAS [1–3, 8, 13–15]. OSAS was found to be related with a decrease in NMCT [16]. Although the interactions between smoking, OSAS and NMCT were clear, the studies that examined NMCT values based on the degree of cigarette dependence, cumulative smoking load and OSAS severity were limited. The aim of this study was to investigate the relationship between NMCT, the degree of smoking dependence, cumulative smoking load and OSAS severity in smokers with OSAS.

Material and methods

This study is controlled, single blind, prospective study and approved by Local Ethical Committee (Ref: 2011-KAEK-25 2018/04-17).

Patients

Patients diagnosed with OSAS in our hospital between April 2018 and April 2019 were examined. All patients aged 18–65 who underwent polysomnography in the sleep laboratory of our hospital were evaluated, and all patients who agreed to participate in the study and did not meet the exclusion criteria were included in the study group (Group 1). A control group was formed according to the demographic characteristics of Group 1 from healthy individuals without OSAS symptoms and history (Group 2).

Exclusion criteria: History of chronic obstructive pulmonary disease; hypertension; hepatic, renal, rheumatological, neoplastic, infectious and endocrine diseases; chronic alcohol use or substance abuse in the past 6 months; usage of antibiotics, antihistamines, antidepressants, anticonvulsants, and antineoplastic drugs; environmental toxins exposure; abnormal ear, nose and throat physical examination (congestion, infection, chronic rhinitis, septal deviation, nasal polyposis); history of nasal surgery; head trauma; malignance; head and neck radiation or chemotherapy; or upper respiratory infections in the past 2 weeks; presence of central nervous

system diseases such as Parkinson or Alzheimer diseases; psychiatric diseases affecting mental status; pregnancy and breast-feeding.

Subjects with OSAS were divided into subgroups as smokers (Group 1a) and non-smokers (Group 1B). Smoking duration, daily smoking rate, cumulative smoking load and the Fagerström nicotine dependency test (FNNDT) were questioned in smokers. The control group was divided into subgroups as smokers and non-smokers (Group 2a and 2b). Smoking duration, daily smoking, cumulative smoking load and the FNNDT were recorded in smokers in Group 2. A saccharin test was applied to groups 1 and 2. The doctor performing the saccharin test did not know in which group and subgroup the patients were.

Complete ear, nose, and throat examinations were performed in order to exclude any sinonasal disease (septal deviation, acute or chronic rhinosinusitis, nasal polyps, etc).

The NMCT values of OSAS in control groups and subgroups; the NMCT and AHI values of smokers and non-smokers with OSAS; the severity of dependence according to the FNNDT, and the NMCT values of smokers with OSAS were compared statistically.

Saccharin test

The saccharin test was discovered by Anderson *et al.* [5] in 1974 and modified by Rutland and Cole [6] in 1980. Subjects were tested early in the morning in a quiet, well-ventilated room. After the nasal secretions were cleaned, a saccharin particle with a diameter of about 1 mm was placed in the subject's nose about 1 cm behind the anterior end of the lower turbinate. The subject was in the sitting position and the head was flexed by 10 degrees. They were asked not to eat, drink or brush their teeth beforehand and try not to cough and sneeze. The moment when the subject first felt the taste in his mouth was noted as mucociliary clearance time [5–7].

Polysomnography

Polysomnography recording simultaneously multiple physiological parameters related to sleep is the gold standard for diagnosis of OSAS [17]. Polysomnography (PSG) was performed using a 58-channel polysomnography device (Compumedics E-Series) on all patients with 4-channel EEG (Electroencephalography), Chin EMG (electromyography), Leg EMG, ECG (electrocardiography), EOG (electrooculography), pulse oximetry, air flow, the combination of thoracic and abdominal respiratory inductance plethys-

Table 1. Smoking data, Polysomnography and NMCT values of Groups 1a and 2a

	Group 1a (n = 58)	Group 2a (n = 37)	p value
Daily cigarettes, median (IQR)	20 (13)	12 (10)	0.99 ^a
Cumulative smoking story (package/year), median (IQR)	19 (25.25)	12 (10)	0.83 ^a
Fagerström Testi, median (IQR)	6.5 (5)	5 (3)	0.65 ^a
Dependence, n (%)			0.24 ^b
Mild	18 (31)	15 (40.5)	
Moderate	21 (36.2)	16 (43.2)	
Severe	19 (32.8)	6 (16.2)	
NMCT [s] median (IQR)	728.5 (622)	660 (240)	0.042 ^{a*}
Mean oxygen saturation [%] median (IQR)	93 (2.25)	94 (2)	0.004 ^{a*}
Oxygen desaturation index [%] ≥ 4 (ODI) median (IQR)	16 (24)	17.5	0.27 ^a

^aMann Whitney-U test; ^bChi-Square test; * p < 0.05. IQR — interquartile rang; NMCT — nasal mucociliary clearance time;

mography (RIP) to provide an accurate representation of the respiratory effort, and snore detecting microphones. The PSG records were evaluated by the specialist doctors certified by the Health Ministry of Turkey, according to the AASM Manual for the Scoring of Sleep and Associated Events Version 2.0. The mean oxygen saturation, Apnea-Hypopnea Index (AHI) and oxygen desaturation index % ≥ 4 (ODI) were evaluated while sleeping.

Apnea-Hypopnea Index

The APNEA-HYPOPNEA INDEX (AHI) is the combined average number of apneas and hypopneas that occur per hour of sleep. If the AHI was 5 or more per hour, OSAS was diagnosed. AHI was categorized as mild OSAS with 5–15/hour, moderate with 15–30/hour and severe with > 30/hour [18, 19].

Fagerström test

The Fagerström test (FNDT) is used to measure nicotine dependence and consists of 6 questions [19, 17]. Physical nicotine dependence is scored on a scale of 1-10 based on the responses of the patient. Subjects were divided into 3 subgroups according to their FNDT scores: mildly dependent (1–4 points), moderately dependent (5–7 points) and severely dependent (8–10 points).

Cumulative smoking load (pack/year)

A pack year is the quantification of cigarette smoking [20, 18]. It is calculated by multiplying the number of cigarette packs smoked per day by the number of years the person has smoked.

Statistical analysis

Statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 23 program. The Kolmogorov-Smirnov test analysed the distribution of the groups. Normally distributed numerical values mean ± standard deviation, distribution of non-normal numerical values median (interquartile range, IQR); categories were evaluated with percentage ratios. A Student t-test and Mann-Whitney-U test were used for comparison of means. An Anova and Kruskal-Wallis test were used in comparison of means of multiple groups. A Chi-Square test was used to compare the ratios. A Spearman correlation test was used for the evaluation of the correlations. P < 0.05 values were considered statistically significant.

Results

The study included 123 subjects with OSAS (Group 1) and 92 healthy controls (Group 2). There were no statistically significant differences between the two groups in terms of age, sex and smoking rates (p = 0.69, p = 0.74, p = 0.31, respectively). Subjects with OSAS had a significantly higher NMCT than the control group (p = 0.005). The number of cigarettes smoked per day, cumulative smoking history, FNDT and NMCT values in Group 1a and Group 2a were shown in Table 1.

There was no statistically significant difference between the groups in terms of daily smoking, cumulative smoking history, the Fager-

Table 2. Values according to OSAS severity in Group 1

	Mild OSAS n = 27	Moderate OSAS n = 51	Severe OSAS n = 45	P-value
Age [years], mean ± standard deviation	49.1 ± 11.6	49.5 ± 9.2	45.9 ± 9.4	0.2 ^a
NMCT [s] median (IQR)	670 (347)	600 (457)	597 (454)	0.55 ^b
Number of cigarettes per day, median (IQR)	10 (12.5)	20 (21.25)	10 (16)	0.31 ^b
Cumulative smoking history [pack/year], median (IQR)	18 (20.5)	23.5 (31.75)	10 (22)	0.55 ^b
Fagerström test, median (IQR)	6 (3.5)	7 (5.5)	5 (6.5)	0.66 ^b
Gender (male), n (%)	20 (76.9)	36 (70.6)	36 (80)	0.55 ^c
Smoking rate, n (%)	17 (65.4)	20 (9.2)	21 (46.7)	0.09 ^c

^aAnova test; ^bKruskall-Wallis test; ^cChi-square test. OSAS — obstructive sleep apnea syndrome; NMCT — nasal mucociliary clearance time; IQR — interquartile range

ström test and addiction severity. The NMCT of smokers with OSAS was statistically significantly longer than the smokers without OSAS. The data of the patients with OSAS who were smokers and non-smokers were compared (Group 1a and Group 1b). The duration of NMCT in smokers was statistically significantly longer than non-smokers ($p = 0.002$). The mean age was significantly higher in Group 1b ($p < 0.001$). There was no significant difference between patients with OSAS who smokers and those who were non-smokers in terms of gender, AHI and ODI ($p = 0.13$, $p = 0.97$ and $p = 0.27$ respectively).

Gender, age and NMCT were significantly different among subgroups of smokers OSAS according to the severity of nicotine dependence ($p = 0.08$, 0.08 and 0.004 , respectively). AHI did not make a statistical difference ($p = 0.49$). When NMCT was found to be significantly different between the three subgroups, the subgroups were also compared in pairs. NMCT of patients with mild dependence was significantly shorter than those with moderate or severe dependence. When the NMCT was found to be significantly different between the three subgroups, the subgroups were also compared in pairs. The NMCT of the patients with mild dependency was significantly shorter than those with moderate or severe dependence ($p = 0.032$, $p < 0.001$, respectively). There was no significant difference between moderate and severe dependent groups ($p = 0.29$).

There was no statistically significant difference in the NMCT between patients who were

divided into three groups according to OSAS severity (AHI value) as mild, moderate and severe (Table 2). The NMCT in patients with mild OSAS was statistically significantly longer than the control group ($p = 0.048$). However, no significant difference was found between moderate and severe OSAS and the control group ($p = 0.27$ and $p = 0.44$, respectively).

In Table 3, we compared the NMCT of smokers and non-smokers in mild OSAS, moderate OSAS and severe OSAS subgroups. The NMCT values of smokers in mild and moderate OSAS were significantly longer than non-smokers. There was no significant difference in severe OSAS.

Again, no significant difference was found between these subgroups in terms of age, daily smoking, cumulative smoking load and the FNMT ($p = 0.65$, $p = 0.35$, $p = 0.68$, $p = 0.71$, respectively).

Patients' smoking status, daily smoking, cumulative smoking history, and the FNMT were correlated with NMCT (*sırasıyla*, $p = 0.001$, 0.007 , 0.014 , 0.001 vs $p = 0.287$, 0.351 , 0.321 , 0.405). There was no correlation between NMCT and OSAS severity ($p = 0.33$).

Discussion

There are studies investigating the relationship between smoking and mucociliary clearance in literature. Studies have shown that long-term smoking causes structural and functional changes in the respiratory system. In addition, epithelial remodelling develops as a result of smoking.

Table 3. Nasal mucociliary clearance time values [s] of smokers and nonsmokers in obstructive sleep apnea syndrome (OSAS) subgroups

	Smokers	Nonsmokers	P-value
Mild OSAS (n = 27)	713 (402)	543 (298)	0.02*
Moderate OSAS (n = 51)	891 (598)	569 (310)	0.01*
Severe OSAS (n = 45)	608 (557)	584 (407)	0.43

*P < 0.05; IQR — interquartile rang

The number of goblet cells increases, and hypertrophy occurs. Silia structure and function of respiratory tract is impaired. An increase in mucus production and a decrease in mucociliary activity result in impaired mucociliary clearance [4, 21].

In various studies, the relationship between smoking and OSAS has been mentioned. Kim *et al* reported that AHI values of male smokers with OSAS were higher than patients with non-smoker OSAS [13]. In a cohort study, the rate of moderate and severe OSAS was found to be higher in smokers than non-smokers [14]. In our study, there was no statistically significant difference between AHI values of smoking and non-smoking OSAS patients. Cigarette smoke contains a wide range of compounds such as chemicals, heavy metals, free radicals and nicotine and has been proposed as a risk factor in OSAS [22]. Mechanisms that explain how smoking may cause OSAS include: (A) Changes in sleep architecture, (B) Neural reflexes caused by nicotine relaxation, (C) Upper respiratory tract muscles relaxation, and (D) Increased awakening threshold in sleep induced by nicotine⁸, increased upper airway inflammation due to inhalation [15].

The most important finding of our study is that there is a significant difference in the NMCT values of the smokers with OSAS according to the subgroup of smoking dependency severity. NMCT values of patients with mild cigarette addiction were shorter than those with moderate and heavy cigarette addicts. No significant difference was found between AHI and subgroup of addictive severity. We believe that our study is important in terms of comparing NMCT and AHI values in OSAS patients according to the severity of smoking dependence. Deniz *et al.* found no significant difference in NMCT in patients with mild to moderate OSAS compared to the control group, but reported that NMCT was significantly prolonged in patients with severe OSAS [16]. In our study, there was no difference in NMCT between subgroups according to OSAS severity. There are not many studies on the effect of OSAS on the upper

respiratory tract. Schrodter *et al.* [23] reported that atrophic epithelium is common in untreated OSAS and ciliary epithelial types are rare. Oxygen desaturation occurs in the nasal mucosal tissue as a result of obstruction in the upper airways. As a result, ultrastructural changes occur and mucociliary clearance is impaired [16]. The NMCT of smokers with OSAS was statistically significantly longer than that of the smokers without OSAS. This finding supported the negative impact of not only smoking but also OSAS on NMCT.

Deniz *et al.* [16] found a statistically significant difference between smokers and non-smokers in terms of mucociliary clearance times in all OSAS groups. In our study, NMCT was significantly longer in smokers with mild and moderate OSAS than in non-smokers. However, no significant difference was found in severe OSAS. Although there was no significant difference in age, cumulative cigarette load, severity of smoking dependency and daily smoking among the subgroups, it was surprising that there was no significant difference between smokers and non-smokers in severe OSAS.

Patients with OSAS were correlated with non-smoking status, daily number of cigarettes, cumulative smoking history and Fagerström dependency test. In this respect, our study supported previous studies [24–26].

Limitations of our study can be listed as follows: Saccharin test was a subjective test due to the patient feeling the taste of saccharin and was considered as a test result when they said that they received the sensation of taste. In addition, since we divided the patient group into three subgroups according to the severity of OSAS and smoking dependence, the sample size of these subgroups was relatively small.

Conclusion

In our study, mucociliary clearance time was significantly higher in smokers with OSAS compared to non-smokers. While OSAS is al-

ready adversely affecting mucociliary clearance, smoking also exacerbates the situation. Smoking in OSAS patients eliminates a very important defence mechanism such as mucociliary clearance of the lungs.

Conflict of interest

None declared.

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