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Serum cfDNA and TNF-α in Adult Men with Obstructive Sleep Apnea

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Abstract

Background: Obstructive sleep apnea (OSA) is a common sleep-related chronic respiratory disorder. There are several factors for characterizing OSA in adults. Two of the potential biomarkers in OSA are cell-free DNA (cfDNA) and tumor necrosis factor-alpha (TNF-α). Some reports indicate that obesity and other variables are likely the major risk factors influencing changes in serum cfDNA and TNF-α levels. Given the controversial role of these two biomarkers, we planned to conduct the present study in male patients with mild OSA and normal body mass index (BMI).

Methods and Results: Two groups of subjects were examined. Group 1 included 195 OSA men. Group 2 included 201 men as normal controls (NC) without OSA. The participants in both groups were aged 51-60 years and had normal BMI in the range of 18.5 to 24.9 kg/m^2. Polysomnography was used to determine the apnea-hypopnea index (AHI) and assess the severity of OSA. The routine ELISA method was used to assess TNF-α and cfDNA in blood serum.

The present report found a significant increase in serum levels of cfDNA and TNF-α in OSA men with normal BMI compared to healthy control men with normal BMI. Still, we did not find a significant correlation between serum cfDNA and TNF-α in the NC and OSA groups.

Conclusion: The role of significantly increased levels of serum cfDNA and TNF-α is evident in OSA men with normal weight BMI. Though both cfDNA and TNF-α show a significant correlation with BMI in obese patients with obstructive sleep apnea, a direct association between cfDNA and TNF-α in normal-weight men with obstructive sleep apnea is not evident. Future studies examining the involvement of key pro-inflammatory and anti-inflammatory biomarkers will clarify the precise roles of serum cfDNA and TNF-α in patients with obstructive sleep apnea.(**International Journal of Biomedicine. 2026;16(2):217-222.**)

Keywords: obstructive sleep apnea • TNF-α • cfDNA • BMI • adult men

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Abbreviations

AHI, apnea-hypopnea index; **AOPPs,** advanced oxidation protein products; **BMI,** body mass index; **cfDNA,** cell-free DNA; **CPAP,** continuous positive airway pressure; **CVDs,** cardiovascular diseases; **dsDNA,** double-stranded DNA; **ELISA,** enzyme-linked immunosorbent assay; **KSA,** Kingdom of Saudi Arabia; **MetS,** metabolic syndrome; **NC,** normal control; **OSA,** obstructive sleep apnea; **OSAHS,** obstructive sleep apnea-hypopnea syndrome; **OSAS,** obstructive sleep apnea syndrome; **TNF-α,** tumor necrosis factor-alpha; **UQU,** Umm Al-Qura University.

Introduction

Obstructive sleep apnea (OSA) is a common sleep-related chronic respiratory disorder[1] that occurs due to repeated episodes of partial or complete upper airway collapse or obstruction during sleep, leading to transient asphyxia or temporary, reversible hypoxia and ischemia. It influences health and quality of life.[2] Obstructive sleep apnea is considered one

of the independent risk factors in various disorders, including cardiovascular diseases (CVDs), neurovascular disorders (e.g., stroke), daytime sleepiness, etc.[3,4]

If daytime sleepiness and daytime-related symptoms appear, the OSA is considered obstructive sleep apnea–hypopnea syndrome (OSAHS) or obstructive sleep apnea syndrome (OSAS).[3] The daytime sleepiness, awakenings with snoring, and restless sleep are the common manifestations with less common symptoms of headaches in the morning, insomnia, mood changes, increased blood pressure or heart rate, weight gain, nocturia, gastroesophageal reflux, erectile dysfunction etc.[5,6] Adolescents or adult people having OSA of long-term go into sleep for a short period if they get rest.[7] Despite the high prevalence of OSA, only about 10% are properly diagnosed.[8] Men are afflicted with OSA more frequently than women, which could be the protective effect of progesterone in women. However, postmenopausal women present a similar frequency of OSA occurrence and have a higher frequency than women in pregnancy.[9] There is a link between body mass index (BMI) and the high prevalence of OSA since an increase in body weight is associated with the development of a higher risk of OSA.[10] The OSA is managed by proper exercise (even without weight loss), weight loss, and avoiding smoking, muscle relaxants, and sedatives. Continuous positive airway pressure (CPAP) is quite effective.[11] Considering prognosis, people with OSA have an increased risk of hypertension, heart attack, congestive heart failure, depression, and diabetes, compared to those without OSA. Cardiovascular diseases and stroke associated with OSA contribute to early death in older adults.[12]

Smoking increases the risk of developing OSA.[3] Some of the medications, including sedatives, and medical conditions of asthma and allergic rhinitis, may complicate the occurrence of OSA.[13] Genetic factors and various phenotypes contribute to the development and progression of OSA.[14] Physiological changes appearing are sleep fragmentation, hypoxia, hyperoxia, and dysfunction of the autonomic nervous system that may lead to inflammatory changes and to clinical consequences.[15] Some of the physiological/metabolic consequences in adults are diabetes, hypertension, ischemic heart disease, obesity, stroke, metabolic syndrome (MetS), etc.[3,16,17]

Biomarkers comprising the genetic factors for the characterization in adults with OSA were studied.[18,19] Cell-free DNA (cfDNA) was studied as a biomarker[20] in inflammation-related disorders.[18,21-26] Several studies have shown an increase in serum/plasma cfDNA in patients with OSA.[27-29] However, no significant change in cfDNA was also investigated in OSA patients compared to controls.[26,30,31] In several studies, increased serum/plasma TNF-alpha (TNF-α) levels have been observed in patients with OSA.[28,32] No change in the levels of TNF-α in patients with OSA compared to controls was also documented, and it was revealed that there is no association of TNF-α and cfDNA in patients with OSA.[26] A report presents an association between TNF-α and pro-inflammatory cytokines, especially in autoimmune diseases,[33] though no clear evidence of a correlation between serum/ plasma TNF-α and cfDNA exists. In view of the limited and controversial information regarding the role of serum/plasma TNF-α and cfDNA, and their association in patients with OSA, we planned the present study.

Materials and Methods

The present case-control study was conducted after obtaining ethical approval (Approval No: HAPO-02-K-012-2022-01-1085) from the College of Medicine of Umm Al-Qura University (UQU), Makkah, Kingdom of Saudi Arabia (KSA). The research work was carried out from Jan 20, 2023, to Dec 20, 2025, at the UQU-associated hospitals/ medical clinics.

The male adult OSA participants were well informed about the purpose and the schedule of collecting their history and blood samples. Detailed interviews were arranged after selecting the patients/control subjects. A comprehensive medical history/physical examination of OSA in adult male patients was performed.

Two groups of subjects were examined. Group 1 included 195 OSA men. Group 2 included 201 men as normal controls (NC) without OSA. The participants in both groups were aged 51-60 years. The participants in both groups in the current study had normal BMI in the range of 18.5 to 24.9 kg/m^2. The sample size was calculated using the calculator and the sample size formula.

Symptoms, including daytime sleepiness, loud snoring, morning headaches, restless sleep, high blood pressure, and high apnea-hypopnea index (AHI) scores, were specifically documented in patients with OSA. The inclusion and exclusion criteria for the various conditions/disorders were established. Exclusion criteria were patients with CVDs, diabetes, MetS, and other serious respiratory disorders, as well as obese and overweight patients.

Polysomnography was used to determine the AHI and assess the severity of OSA. To determine AHI, the total number of apnea and hypopnea episodes/events was divided by the total sleep hours. Episodes of apnea and hypopnea were considered as such if they lasted at least 10 seconds. The OSA diagnosis in adults is defined by an AHI exceeding 5 events per hour, leading to daytime sleepiness (mild: 5-<15; moderate: 15-<30; severe: ≥30 with fatigue). The present study examined mild cases of OSA (AHI: >5–<15), as well as subjects in a control group (NC) (AHI: ≤5). Routine ELISA (Enzyme-Linked Immunosorbent Assay) method was used to assess TNF-α and cfDNA in blood serum.

The IBM SPSS Statistics (version 24.0, IBM Corp., Armonk, NY) and GraphPad Prism (version 6.0, San Diego, CA, USA) software were used for data analysis. The mean±SEM were the values for the unpaired t-test analysis for obtaining two-tailed p-values. The linear correlation was analyzed by plotting the regression lines and obtaining R2 and corresponding p-values. The *P*-value of ≤0.05 was considered the threshold level showing a significant difference.

Results

Mean age in the OSA and NC groups were 55.51±0.20 and 55.39±0.20 years, respectively (*P*=0.67). The BMI values

in the OSA and NC groups were 21.89±0.15 and 21.81±0.15 kg/m^2, respectively (P=0.69).

Serum TNF-α level in NC and OSA groups was 5.19±0.29 and 9.42±0.52 pg/mL, respectively (P<0.001) (Fig.1). Serum level of cfDNA in NC and OSA groups was 114.50±4.76 and 186.65±8.03 ng/mL, respectively (P<0.001) (Fig.2).

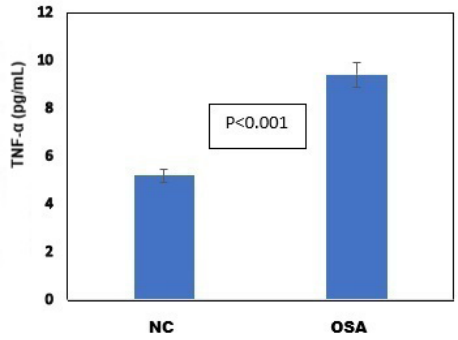

Fig.1. *Serum TNF-α in adult men with OSA and NC adult men with normal BMI.*

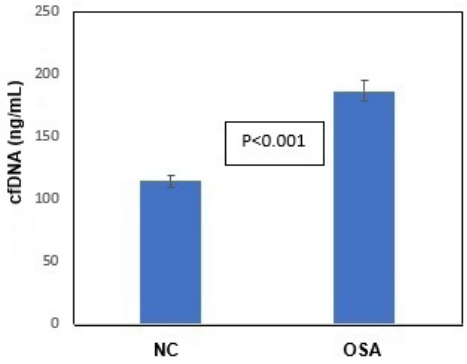

Fig.2. *Serum cfDNA in adult men with OSA and NC adult men with normal BMI.*

The NC group showed a non-significant association between BMI and serum TNF-α (R^2=0.005, P=0.30). In the OSA group, we found a significant weak positive association between BMI and TNF-α (R^2=0.033, P=0.01). The NC group showed a non-significant association between BMI and serum cfDNA (R^2=0.000, P=0.89). In the OSA group, a significant weak positive association between BMI and cfDNA (R^2=0.024, P=0.03) was found. The associations of BMI with TNF-α and cfDNA in the study groups are shown in Table 1.

Table 1.

Association of BMI with serum TNF-α and cfDNA in study groups.

Variable	Groups	Association of BMI with TNF-α and cfDNA		
		R^2	df	P-value
TNF-α	NC	0.005	199	0.30
	OSA	0.033	193	0.01
cfDNA	NC	0.000	199	0.89
	OSA	0.024	193	0.03

BMI, body mass index; TNF-α, tumor necrosis factor-alpha; cfDNA, cell-free DNA; NC, normal control; OSA, obstructive sleep apnea; R^2, coefficient of determination.

Table 2 presents the association between serum TNF-α and cfDNA. The slope, intercept, R^2, and P-value indicate that the association between TNF-α and cfDNA was not significant in both groups.

Table 2.

Association between serum TNF-α and cfDNA in study groups.

Groups	Association between serum TNF-α and cfDNA				
	Slope	Intercept	R^2	df	P-value
NC	1.25	108.03	0.006	199	0.28
OSA	0.97	105.31	0.010	193	0.16

TNF-α, tumor necrosis factor-alpha; cfDNA, cell-free DNA; NC, normal control; OSA, obstructive sleep apnea; R^2, coefficient of determination.

Discussion

Oxidative stress-related lipid and DNA oxidation have been reported in previous studies in obstructive sleep apnea. Ozben et al.[20] showed that high systemic oxidative stress in obstructive sleep apnea is associated with increased levels of advanced oxidation protein products (AOPPs). The connection between AOPPs, β-globin, and ischemia in OSA highlights a cascade of oxidative stress that leads to molecular damage, including DNA fragmentation (often assessed by cfDNA or nucleosome levels). Studies of cfDNA indicate that, while healthy individuals exhibit low levels of cfDNA in blood serum, patients with OSA demonstrate significantly elevated concentrations—often measured using the β-globin (HBB) gene as a marker.[20]

An oxidative stress biomarker, cfDNA, at high levels serves as a biomarker in several inflammation-related diseases, including autoimmune diseases, ischemic heart disease, stroke, cancer, acute coronary syndrome, and OSA.[18,21-25]

While investigating the best global tests for characterization, OSA patients showed elevated plasma cfDNA levels.[29] It was found that cfDNA, which is released in apoptosis and shows elevated levels in cardiovascular diseases, cancer, and other disorders, was significantly higher in severe OSA than in subjects with mild to moderate OSA and those without OSA.[30] Furthermore, it was revealed that OSA-related free radicals cause degradation and destruction of fragmented nucleic acid-DNA, and resultantly, high levels of cfDNA and nucleosomes are found.[36,37] Higher levels of cfDNA were obtained in OSA vs. healthy controls,[27] showing linear correlation with the OSA severity.[33] The patients with severe and moderate OSA presented higher outcomes than those with mild OSAS.[38] Furthermore, double-stranded DNA (dsDNA) and nucleosome levels were higher in OSA patients than in the control healthy subject group.[28] While studying several biomarkers of endothelial function/damage in OSA patients in baseline and after 3-month therapy of CPAP, it was revealed that circulating cfDNA increased significantly.[39]

The above-mentioned reports provide extensive evidence for the results for serum cfDNA obtained in the present study. However, OSA patients with AHI > 30 showed higher plasma DNA levels, but no significant difference was

observed between mild-to-moderate OSA patients with AHI 5-30.[30] We suggest that the study of the collective effects of 5-30 AHA shows the presentation of collective variations not explainable logically. Additionally, DNA damage and oxidative stress were not found in another study of patients with OSA.[31] In view of these findings, we suggest that the criteria, methodology, and scenario of the mentioned studies were different and that this was most likely the reason behind the non-significant change of cfDNA in OSA patients compared to their well-matched controls.

Several pro-inflammatory cytokines, including TNF-α, were also found to be increased in OSA.[28] The TNF-α postoperative levels at the third month decreased significantly compared to preoperative levels under the expansion sphincter pharyngoplasty for OSA patients, which explains the role of TNF-α in OSA patients.[32] Other studies also reveal that the adult patients with OSA showed significantly higher levels of TNF-α compared to healthy and age-matched control subjects.[40,41] This indicates a strong association between OSA and systemic inflammation.[42] This is evident from the investigation that a healthy weight loss lifestyle lowered the plasma levels of TNF-a in OSA patients.[42] These observations are in accordance with our results in the present study.

On the other hand, there are several studies showing a non-significant difference of TNF-α in OSA patients compared to controls, mainly due to obesity/ overweight status instead of apnea[41,43] The subgroup analysis showed no significant difference in plasma TNF-α levels between OSA and control adult subjects with BMI ≤ 30 kg/m².[41] No significant change in TNF-α is due to the confounding factors, mainly obesity, differences in sample size, detection methods, study design, and diurnal rhythms.[41,44,45]

Serum/plasma levels of cfDNA associate positively with pro-inflammatory cytokines, especially in autoimmune diseases.[33] Another report reveals a concomitant increase in cfDNA and TNF-α in OSA.[28] On the other hand, it is known that CPAP therapy or moderate intensity physical activity for OSA patients influences cfDNA and several inflammatory biomarkers, including TNF-α. However, short-term treatment with medium- to long-term CPAP or aerobic exercise therapy in moderate-to-severe OSA patients did not alter blood levels of cfDNA or TNF-α.[26] This report and some of the other cited reports explain that obesity and other variables are most likely the major risk factors influencing the change in serum cfDNA and TNF-α levels. Since we studied OSA patients with normal-weight BMI in the present study. The present report found a significant increase in serum levels of cfDNA and TNF-α in OSA men with normal BMI compared to healthy control men with normal BMI. Still, we did not find a significant correlation between serum cfDNA and TNF-α in the NC and OSA groups. The present study emphasizes the need for further studies to better understand the roles of relevant inflammatory markers in interpreting the net contribution of serum cfDNA and TNF-α, as well as their association with each other in OSA patients with normal-weight, overweight, and obese subjects. There are some studies that suggest limitations, corrections for comorbidities, study design, sample size, methodological limitations, diurnal rhythms, or different scenarios in patients with mild-to-moderate OSA, and therefore, it is possible that there is no significant correlation between serum/plasma levels of cfDNA and TNF-α in OSA patients.

Conclusion

The role of significantly increased levels of serum cfDNA and TNF-α is evident in OSA men with normal weight BMI. The cfDNA is a biomarker for ischemia and hypoxia. Though both cfDNA and TNF-α show a significant correlation with BMI in obese patients with obstructive sleep apnea, a direct association between cfDNA and TNF-α in normal-weight men with obstructive sleep apnea is not evident. Future studies examining the involvement of key pro-inflammatory and anti-inflammatory biomarkers will clarify the precise roles of serum cfDNA and TNF-α in patients with obstructive sleep apnea.

Ethical Considerations

The study was carried out in accordance with ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Ethical Committee of the Faculty of Medicine, Umm Al-Qura University (UQU); Approval Number: "HAPO-02-K-012-2022-01-1085." Written informed consent was obtained from all participants.

Author Contributions

Waheeb Alharbi: Supervision, Conceptualization, Investigation, Writing – review and editing.
Ahmad H. Mufti: Conceptualization, Investigation, Data curation. Formal analysis, Writing – original draft.

All authors have approved the final article.

Conflict of Interest

The authors have declared no conflict of interest.

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