

Examination of the Relationship Between Metabolic Syndrome and Obstructive Sleep Apnea in Iranian Patients with Type 2 Diabetes: A Case–Control Study

This article was published in the following Dove Press journal:
Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

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Introduction: Obstructive sleep apnea (OSA) is a common risk factor for metabolic syndrome (MS) that increases the chance of cardiovascular disease, stroke, and mortality. Many studies have been conducted on this matter, but the results are still conflicting. The aim of the present study was to examine the relationship between metabolic syndrome (MS) and obstructive sleep apnea (OSA) in Iranian patients with type 2 diabetes (T2D).

Patients and Methods: This matched case–control study was conducted with 190 patients with T2D in Sanandaj, Iran. The data were selected using the demographic questionnaire, clinical and anthropometric measures, the Berlin Questionnaire (BQ), and the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III). Participants were divided into two groups of high risk of OSA (experimental) and low risk of OSA (control). The data were analyzed using Stata, version 14.

Results: The frequency of MS was higher in the OSA group than the control group (81.1% vs 70.5%), but the group difference was not statistically significant ($p=0.127$). The results of crude and age-sex adjusted logistic regression analysis revealed no significant association between OSA and the other variables under study ($P>0.05$). Sensitivity analysis and external adjustment for BMI showed no significant relationship between OSA and the other variables under study ($P=0.319$).

Conclusion: In the present study, no significant association was found between metabolic syndrome (MS) and obstructive sleep apnea (OSA) in patients with T2D; therefore, more studies should be conducted on this subject.

Keywords: diabetes, sleep apnea, metabolic syndrome

Introduction

The high prevalence of diabetes and its complications has become a major global health issue.¹ Currently, about 425 million people around the world suffer from diabetes, and this figure is projected to grow to 629 million people by 2045.² There is an increase in the prevalence of diabetes in Iran, and it is projected that 7 million people in this country will have diabetes by 2030.³ Diabetes is accompanied by various complications, including great vessels problems (eg, cardiovascular disease), small vessels problems (eg, retinopathy), and other complications, such as skeletal, digestive, liver, and cognitive problems.^{4,5} It has also been shown that OSA in diabetic patients puts them at higher risk for major adverse cardiac and cerebrovascular events (MACCE) and cardiovascular mortality.⁶

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It is a treatable chronic sleep disorder that is characterized by recurrent episodes of partial (hypopnea) or complete (apnea) collapse of the upper airway, leading to transitory episodes of hypercapnia, repeated micro-awakenings, and desaturation–reoxygenation sequences.^{7,8} OSA is related to poor glycemic control,^{9–11} high blood pressure,¹² and lower quality of life.^{13,14} Some researchers maintain that OSA is not just a sleep disorder, but a heterogeneous metabolic disorder related to some other disorders, including fatty liver disease,^{15–17} hypothalamic-pituitary-adrenal (HPA) axis dysfunction, endothelial dysfunction, neurological disorders, reduced cognitive capacity, depression, elevated inflammatory markers such as C-Reactive Protein (CRP) and interleukin-6, intensification of tissue hypoxia, higher risk of systematic inflammations, heart failure, dysregulation of cardiac metabolism, dysrhythmia, cardiac conduction disturbances, atrial enlargement, and finally death.^{18–23}

One of the disorders considered to be related to OSA is metabolic syndrome (MS) that is a collection of risk factors, including central obesity, hypertension (HTN), insulin resistance, and dyslipidemia.^{24,25} MS has a high prevalence throughout the world, and it is projected that half of the world's population will be struggling with that in the coming years.^{26–28} According to previous reports, MS has prevalence rates of 20–40% and 29% in the world and Iran, respectively.^{29,30,31} MS increases the risk of cardiovascular disease by 78%, diabetes by 500%, stroke by 75%, and mortality by 35%.^{32–34}

The relationship between OSA and MS is still debatable, and previous studies have reported conflicting results.^{35–37} Some studies have found an association between OSA and MS,^{38–47} while others have failed to find a relationship between the two variables or have found associations between OSA and some components of MS.^{48–50} The relationship between OSA and MS is important because the co-occurrence of these two conditions in patients with type 2 diabetes (T2D) leads to more severe diabetes complications, increased blood pressure, higher lipid levels, increased c reactive protein levels, and reduced sleep quality,^{37,48–51} all of which are risk factors for cardiovascular disease. Given the conflicting results on the relationship between the two variables, the goal of the present study is to examine the relationship between MS and OSA among patients with

T2D attending the diabetes unit of Tohid Hospital in Sanandaj in 2019.

Patients and Methods

Study Participants

This is a matched case–control study. The participants included 190 patients with T2D who were selected using a convenience sampling method among patients attending the diabetes unit of Tohid Hospital in Sanandaj in 2019. The cases were with OSA, and the controls were without this condition. The inclusion criteria were as follows: having a medical record in the diabetes unit and the ability to communicate. The exclusion criteria included lack of interest to continue the study and incomplete questionnaires.

Data Collection

After receiving the approval of the ethics committee at Kurdistan University of Medical Sciences, the researchers attended the diabetes unit and explained the study objective and procedures to the participants and acquired their informed consents to participate in the study. For diabetic patients receiving service from the diabetes unit, medical tests are done every 3 months, and the results are recorded in medical records. Therefore, the results of the most recent lipid and blood sugar tests were extracted from the medical records and recorded in the questionnaires. In order to ensure confidentiality, medical record numbers were put on top of the questionnaires instead of participants' real names. In addition to medical record number, demographic information, including age, gender, marital status, place of residence, insurance status, education, duration of diabetes, medications used, and anthropometric measurements, including waist circumference, height, weight, BMI, and blood pressure were recorded. Waist circumference was measured at the level of the umbilicus using an inflexible measuring tape, with the participant in a standing position and wearing light clothing. BMI was calculated by dividing weight by height square. In addition, blood pressure was measured using Beurer BC40 Wrist Blood Pressure Monitor after 5 mins resting in the sitting position.

OSA Questionnaire

Although polysomnography is often the gold standard in the diagnosis of OSA, it is not widely used due to being costly and time-consuming.⁴³ In the present study, due to lack of access to a sleep clinic, the Berlin Questionnaire was used to screen OSA. Different instruments are

available to screen sleep apnea used in different studies. After a review of the literature to find the best screening tool for sleep apnea, we decided to use the Berlin Questionnaire. In a study among Iranian patients, Amra et al (2018) compared different screening tools for sleep apnea and found that the Berlin questionnaire had higher sensitivity than the STOPBANG.⁵² A systematic review by Abrishami et al (2010) also indicated that the Berlin questionnaire had higher sensitivity than the STOPBAN.⁵³ Berlin Questionnaire has 10 items assessing three domains, including snoring (items 1–5), daytime sleepiness (items 6–9), and hypertension or a high BMI (item 10).^{43,54} The researcher read the items for the illiterate participants and recorded their answers in the questionnaire. Based on the completed questionnaires, participants were divided into two groups of “at a high risk for OSA (cases)” and “at a low risk for OSA”. The sample included 95 patients who were matched in gender and BMI. The validity of the questionnaire in Iran has been shown by Ghanei Gheshlagh et al (2011).³⁹ Before the main sampling, the Berlin questionnaire was administered to a sample of 20 diabetic patients in Sanandaj (who were not included in the main study) in order to examine the reliability and internal consistency (using the Cronbach’s alpha coefficient). The internal consistency of the questionnaire using the Cronbach’s alpha coefficient was found to be 0.73.

Metabolic Syndrome: Diagnostic Criteria

The National Cholesterol Education Program Adult Treatment Panel guidelines III (ATP III) was used to assess MS, according to which MS is diagnosed if at least three of the following criteria are met: hyperglycemia (fasting blood sugar level ≥ 110 mg/dl), dyslipidemia (triglyceride (TG) level above 150 mg/dl, high-density lipoprotein (HDL) cholesterol level below 40 mg/dl in men and below 50 mg/dl in women), obesity (waist circumference ≥ 102 cm in men and ≥ 88 in women), and blood pressure $\geq 130/85$ mmHg.⁵⁵

Data Analysis

Descriptive statistics, including frequency, frequency percentage, mean, and standard deviation, were used to describe the data. Qualitative variables were described by frequency and frequency percentage, and were compared between the OSA and control groups using the Chi-squared test. The relationship between OSA and other variables under study was examined by the crude and age-

sex adjusted of odds ratio and their 95% confidence intervals using logistic regression as well as penalized logistic regression. In order to ensure the stability of the results, sensitivity analysis with additional adjustment for the MBI variable was conducted. All the analyses were performed using Stata, version 14.

Results

Participants with and without OSA were matched in gender and age (± 5). There was no significant difference between the two groups in demographic variables and components of MS. Duration of diabetes was 13.2 ± 9.1 years and 11.4 ± 8.9 years in the experimental and control groups, respectively ($p=0.183$). Further details are provided in Tables 1 and 2.

In order to examine the association of OSA with MS and other variables under study, the logistic regression analysis was conducted, and the crude rate of odds ratio was calculated for each variable (Table 3). In the next step,

Table 1 Demographic Characteristics

Variables		OSA (n=95)	Control (n=95)	p-value
Marital situation	Single	18 (18.9)	73 (76.8)	0.594
	Married	77 (81.1)	22 (23.2)	
Literacy	Illiterate	59 (62.1)	66 (69.5)	0.278
	Primary	24 (25.3)	18 (18.9)	
	High school	6 (6.3)	9 (9.5)	
	University	6 (6.3)	2 (2.1)	
Residency	Urban	89 (93.7)	90 (94.7)	0.990
	Rural	6 (6.3)	5 (5.3)	
Health insurance	Yes	80 (84.2)	77 (81.1)	0.702
	No	15 (15.8)	18 (18.9)	
Income	Good	14 (14.7)	14 (14.7)	0.982
	Moderate	63 (66.4)	64 (67.4)	
	Bad	18 (18.9)	17 (17.9)	
Occupation	Yes	77 (81.1)	81 (85.3)	0.561
	No	18 (18.9)	14 (14.7)	
Cigarette	Non-smoker	82 (86.3)	90 (94.7)	0.137
	Former smoker	7 (7.4)	3 (3.2)	
	Smoker	6 (6.3)	2 (2.1)	
Drug	Insulin	27 (28.4)	34 (35.8)	0.321
	Pills	42 (44.2)	43 (45.3)	
	Insulin + pills	26 (27.4)	18 (18.9)	

Table 2 Components of Metabolic Syndrome

Variables	OSA Patients (n=95)	Controls (n=95)	p-value
BMI	28.7±3.5	27.5±3.2	0.013
Waist circumference	102.4±13.7	99.7 ± 8.0	0.097
Systolic blood pressure (mmHg)	134.2±19.5	131.4±21.9	0.362
Diastolic blood pressure (mmHg)	87.1±12.4	76.5±12.5	0.371
HDL-cholesterol, (mg/dl)	55.5±22.2	62.9±32.5	0.069
Triglycerides, (mg/dl)	193.5±87.5	176.7±74.4	0.157
Fasting plasma glucose, (mg/dl)	172.0±56.2	173.6±59.9	0.853

Table 3 Association Between OSA and Other Variables Under Study Analyzed Using the Univariate Regression Analysis

Variables		Crude OR (95% CI)	P-value
MS	Yes	Reference	0.092
	No	0.560 (0.28–1.10)	
Smoking status	Non-smoker	Reference	0.199
	Former smoker	2.35 (0.64–8.65)	
	Smoker	2.85 (0.64–12.64)	
Place	Urban	Reference	0.766
	Rural	1.19 (0.37–3.86)	
Education	Illiterate	Reference	0.271
	Primary	1.48 (0.74–2.97)	
	High school	0.76 (0.26–2.20)	
	University	2.9 (0.65–13.02)	
Job	Un-employed	Reference	0.439
	Employed	1.35 (0.63–2.90)	
Marriage	Married	Reference	0.717
	Single	0.88 (0.43–1.78)	
Income	Low	Reference	0.849
	Moderately	0.93 (0.35–2.55)	
	High	0.94 (0.44–1.96)	
Drug	Insulin	Reference	0.539
	Pill	1.23 (0.64–2.38)	
	Insulin and pill	1.81 (0.83–3.99)	
Duration of diabetes		1.02 (0.99–1.05)	0.185

variables with p-values below 0.2 were included in the multivariate regression analysis.

In the multivariate analysis using the crude and age-sex adjusted of odds ratio and their 95% confidence intervals, the relationship of OSA with MS and the other study variables was examined using the ordinal logistic

regression and the penalized likelihood method for logistic regression. In order to ensure the stability of the results, sensitivity analysis with additional adjustment for the BMI variable was conducted. In the multivariate analysis, no significant association was found between OSA and MS with adjustment for age and sex; this was also true for the other variables present in the model. In the sensitivity analysis (with adjustment for age, gender, and BMI) no significant association was found between OSA and MS and also between OSA and the other variables present in the model (p-value >0.05) (Table 4).

Discussion

The results showed no significant difference between the two variables; this finding is consistent with those of studies conducted in Turkey and Greece.^{49,56} Chin et al (2010) also found no significant association between the severity of OSA and MS after adjusting for age and BMI.⁴⁸ This finding can be attributed to certain aspects of diabetes. In other words, due to overlapping characteristics, both MS and OSA can independently lead to diabetes.

In contrast to our finding, some other studies have found a significant relationship between MS and OSA.^{38,40,41,45} This relationship can be attributed to intermittent hypoxia and oxidative stress due to OSA that leads to resistance to insulin, dyslipidemia, and hypertension through secretion of inflammatory cytokines, tumor necrosis factor (TNF), and interleukin 6.^{57–60} On the other hand, lipid deposition occurs in the pharyngeal tissue and is narrowed in the area of upper airway collapse.⁶¹ In addition, there is a strong overlap between the pathophysiology of MS and that of OSA.⁶² Moreover, Leon et al reported a positive association between lung function impairment and MS.⁶³ Contracting findings from previous studies can be attributed to the use of samples with different demographic and clinical characteristics and the use of different instruments to measure MS and OSA. In the present study, no significant difference was found between diabetic patients with and without OSA in MS; this finding is in line with those of Trombetta et al (2010) and Ahabab et al (2013).^{50,56} Given that the study participants had diabetes, the difference between the experimental and control groups in blood glucose levels can be considered noteworthy. However, other studies have found higher levels of blood sugar,^{37,49} systolic blood pressure,^{33,64} waist circumference,⁵⁴ and triglyceride in patients with

Table 4 Multivariable Regression Logistic

Variables		Multivariable Analysis	P-value	Sensitivity Analysis	P-value
		Adjusted OR (95% CI) ^a		Adjusted OR (95% CI) ^b	
MS	Yes	Reference	0.130	Reference	0.319
	No	0.579 (0.285–1.175)		0.691 (0.33–1.43)	
Smoking status	Non-smoker	Reference	0.114	Reference	0.173
	Former smoker	3.268 (0.751–4.217)	0.166	2.81 (0.63–12.44)	0.282
	Smoker	3.082 (0.627–15.140)		2.40 (0.48–11.95)	
Education	Illiterate	Reference	0.147	Reference	0.110
	Primary school and middle school	1.940 (0.793–4.744)		2.10 (0.84–5.24)	
	High school and diploma	1.147 (0.325–4.052)		1.14 (0.32–4.10)	
	University	3.161 (0.607–16.454)		1.31 (0.63–17.42)	
Drug	Insulin	Reference	0.397	Reference	0.408
	Pill	1.346 (0.676–2.678)		1.34 (0.67–2.70)	
	Insulin and pill	1.585 (0.703–3.574)		1.73 (0.76–3.96)	
Duration of diabetes		1.026 (0.988–1.065)	0.186	1.03 (0.99–1.10)	0.138

Notes: ^aAdjusted for age and sex. ^bAge, sex, and BMI.

OSA than those without this condition. In Drager's study, all components of MS, except for waist circumference and HDL, were higher in patients with OSA than those without this condition.³⁷ Wang et al (2019) also found that all components of MS, except for diastolic blood pressure and HDL, were higher in the group with OSA than the control group.¹⁷

One of the limitations of the present study was the lack of access to polysomnography as the golden standard for OSA diagnosis. In addition, patients with OSA may not be aware of their problem, and this may have affected their answers to the items of the questionnaires. Moreover, given that the study was conducted with patients with T2D, caution should be taken in generalizing the results in the general population or other populations of patients. We suggest future studies to use polysomnography to screen OSA or use it along with other tools.

Conclusion

In the present study, no significant relationship was found between metabolic syndrome (MS) and its components in patients with T2D; thus, it seems necessary to conduct more studies on this subject. In addition, medical teams should pay special attention to the presence of these two conditions, whether together or independently, in patients with diabetes, because it leads to an increased chance of morbidity and mortality in the patients.

Acknowledgments

The researchers would like to express their gratitude to the Deputy of Research of the Kurdistan University of Medical Sciences for acceptance, and approval of this research project. We also thank all the diabetic patients and staff of Sanandaj Diabetes Unit.

Disclosure

The authors report no conflicts of interest in this work.

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