

The Association Between OSA and Glycemic Control in Diabetes

Abstract

Background: Obstructive sleep apnea (OSA) is the most common sleep-related respiratory disorder. It is frequently comorbid with cardiovascular, cerebrovascular, and metabolic diseases and is commonly observed in populations with these comorbidities. Investigators aimed to assess the effect of OSA on glycemic control in patients with diabetes. **Methods:** In this cross-sectional study, 266 adult patients with diabetes mellitus (DM) attending the outpatient endocrinology clinic at the Guilan University of Medical Sciences were enrolled. Patients completed a checklist that included demographic characteristics, factors, and laboratory results in addition to Berlin and STOP-BANG questionnaires to evaluate the risk of OSA. Data were analyzed by independent *t*-test, Mann-Whitney *U* test, and Chi-squared or Fisher's exact tests using the Statistical Package for the Social Sciences (SPSS) version 17. **Results:** A total of 266 patients with DM were enrolled in this study (34.6% males, mean age 47.00 ± 19.04 years). Based on the Berlin Questionnaire, 38.6% of all participants were at high risk of developing OSA. Based on the STOP-BANG Questionnaire (SBQ), 45.1% were at moderate and high risks. Additionally, this questionnaire showed a significant difference between low and moderate-to-severe groups regarding sex, age, body mass index (BMI), neck size, other chronic diseases, types of DM, use of insulin, Berlin Questionnaire, fasting blood sugar (FBS), and mean HbA1c. **Conclusions:** Based on the SBQ, our results indicated a significant relationship between OSA and glycemic control according to mean HbA1c and FBS. Therefore, by controlling the OSA, we may find a way to achieve better glycemic control in diabetic patients.

Keywords: Adult, apnea, diabetes mellitus, sleep

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder caused by increased blood glucose due to insufficiency or inefficiency of insulin.^[1] It is one of the most significant global health emergencies of the twenty-first century that does not respect borders or social classes. In 2017, the International Diabetes Federation estimated that the prevalence of DM was almost 451 million and is expected to increase to 693 million by 2045.^[2] It has several complications, and among the complications so far, sleep disorders and obstructive sleep apnea have been less noticed.^[3]

Obstructive sleep apnea (OSA) is the most common sleep-related respiratory disorder, with a high prevalence linked to increased obesity. OSA is frequently comorbid with cardiovascular, cerebrovascular, and metabolic diseases and is commonly observed

in populations with these comorbidities.^[4] The relationship of OSA with these multisystem disorders may be bidirectional. OSA may contribute independently to insulin resistance (IR) and glucose dysmetabolism through its pathophysiological profile of intermittent hypoxia, sympathetic activation, oxidative stress, and inflammation.^[5]

Besides, chronic intermittent hypoxia (IH) can increase free fatty acid (FFA) release, leading to ectopic fat deposition in the liver and muscle resting in IR.^[6] The impacts of chronic IH and oxidative stress on IR could also be mediated by hypoxia-inducible factor (HIF) tissue effects.^[7] The increase in insulin resistance contributes to the severity of OSA. In a previous study on patients without diabetes, patients with moderate-to-severe OSA had a lower β -cell function compared to healthy controls; and a higher apnea-hypopnea index (AHI) was associated with lower β -cell function despite adjustment for obesity.^[8]

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Current investigations are dominated by studies assessing the action of OSA on glucose homeostasis and DM. However, the possibility of diabetic autonomic neuropathy as a predisposing factor toward sleep-related pharyngeal collapse and OSA has been raised. It is noted that in normal-weight patients with DM, there was a higher prevalence of OSA than in the general population. This limited result raised the possible contribution of autonomic neuropathy.^[4] Additionally, epidemiological studies have suggested that obesity is increasing in patients with type 1 diabetes mellitus (T1DM), which might further increase their risk of developing OSA.^[9]

Furthermore, other factors might contribute to the high prevalence of OSA in children and adolescents with T1DM, including lower mean lung volumes and impaired gas exchange with lower diffusing capacity for carbon monoxide.^[10] There are similar findings of impaired pulmonary function in adult patients with T1DM.^[11–13] As the natural history, impact, and pathogenesis of OSA in patients with T1DM remain poorly explored, large and well-designed studies are needed.^[9] Although we have diverse patients who obey a healthy lifestyle and know how to calculate carbohydrates, managing DM is still challenging for clinicians. It seems that other parameters may be involved in the management. As in our previous published article, we found a significant association between sleep quality and glycemic control^[14]; therefore, investigators aimed to assess the association between the risk of OSA and glycemic control in patients with by exploring the association between glycemic control and OSA, we may find a way to achieve better glycemic control in diabetic patients.

Material and Methods

Participants

In this cross-sectional study, 266 adult patients with T1DM and T2DM attending the outpatient endocrinology clinic of Guilan University of Medical Sciences were enrolled. They were referred for their regular follow-ups from January 2019 to January 2020. Patients were recruited by convenient sampling based on their previous diagnosis of DM by an endocrinologist regarding their symptoms and paraclinical factors. The exclusion criteria were previously diagnosed sleep disorders due to the patients' self-statement, uncontrolled psychiatric disorders and use of antipsychotic medications, gestational diabetes, age <18 years, traveling across time zones in previous months, and chronic use of glucocorticoids. Written and informed consent letters were obtained from the participants. Ethical approval was obtained from the ethics committee of the Vice-Chancellor of Research at Guilan University of Medical Sciences (Number: IR.GUMS.REC.1398.401, date: 2019-11-09).

Study design

Patients completed an online checklist including demographic and disease-related characteristics, laboratory

results, and questionnaires to evaluate the risk of OSA. Demographic characteristics were age, sex, education, job, marital status, weight, height, and neck size. Body mass index (BMI) was calculated based on self-reported weight and height by the formula of weight (kg)/height² (m²). The disease-related characteristics included the type of DM, other chronic diseases, types of treatment and medications, DM-related complications, and duration of DM. The checklist asked about diabetes-related complications such as retinopathy, neuropathy, and nephropathy. We conformed the patients' statements about disease-related data with registered files and physicians' examinations. Laboratory results were glycosylated hemoglobin (HbA1c) and fasting blood sugar (FBS). We referred the patients to specific and reliable laboratories for measuring HbA1c. These laboratories had the same methods of measurement and used the same kits. Additionally, the risk of OSA was assessed based on the Berlin and STOP-BANG questionnaires.

We determined the poor and good glycemic control categories based on the seven cutoff points of HbA1c.^[15]

Assessment of subjective sleep characteristics

Berlin questionnaire

The Berlin Questionnaire (BQ), one of the most well-known instruments for evaluating subjects at high risk of OSA, was first introduced by Netzer *et al.*^[16] in Berlin, Germany. It has ten questions in three categories. In category 1, high risk is defined as persistent symptoms (3–4 times/week) in two or more questions about their snoring. In category 2, high risk is defined as persistent (3–4 times/week) sleepiness, drowsy driving, or both. In category 3, high risk is defined as a history of high blood pressure (BP) or a BMI of more than 30 kg/m². The high-risk group was considered if a patient had high-risk results in at least two categories mentioned above. Those with temporary and non-persistent symptoms or only one high-risk category were placed in the low-risk group.

The reliability and validity of the Persian version of this questionnaire were assessed by Amra *et al.*,^[17] Sadeghniai-Haghighi *et al.*,^[18] and Khaledi *et al.*^[19] Amra *et al.*^[17] reported Cronbach's α as 0.7 for the first section and 0.5 for the second section of the questionnaire.

STOP-BANG questionnaire

The STOP-BANG questionnaire (SBQ) is a concise and effective OSA screening tool first introduced by Chung *et al.*^[20] It consists of eight dichotomous (yes/no) items related to the clinical features of sleep apnea. The total score ranges from 0 to 8. Patients are classified for OSA risk based on their respective scores. The questions obtain information on snoring, tiredness, observed apnea, high BP, BMI, age, neck circumference, and male gender (STOP-BANG). Patients with a SBQ score of 0–2 are classified as low risk for moderate-to-severe OSA, whereas those with a score of

5–8 are classified as high risk for moderate-to-severe OSA. In patients with the midrange (3 or 4) SBQ scores, further criteria are required for classification. The reliability and validity of the Persian version of this questionnaire were assessed by Sadeghniaat-Haghighi *et al.*^[21]; they reported that it was a valid and reliable tool with similar results to its original version.

Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software version 17.0.2 (Chicago, IL, USA). Descriptive characteristics of qualitative variables were reported by frequency and percentage. The Shapiro–Wilk test was used to determine the normality of the distribution. Results for continuous variables were demonstrated as mean ± standard deviation (SD), and continuous variables without normal distribution were demonstrated as median (interquartile range [IQR]). The normal and non-normal distributed quantitative variables were assessed by an independent *t*-test or Mann–Whitney *U* test. The Chi-squared test or Fisher’s exact test was used to compare categorical variables. A *P* value < 0.05 indicated statistical significance.

Results

A total of 266 patients with DM were enrolled in this study (34.6% males, mean age being 47.00 ± 19.04 years). Forty point two percent of the participants had T1DM, and 59.8% had T2DM. The mean age, BMI, and DM duration in patients with T1DM were 28.55 ± 11.49, 23.76 ± 4.06, and 13.26 ± 8.04, respectively. In contrast, these parameters in T2DM patients were 59.11 ± 11.78,

28.33 ± 5.26, and 28.33 ± 5.26, respectively. Almost all T1DM patients use insulin, whereas only 26.1% of T2DM patients use it. The diabetes-related complications in T1DM and T2DM were 17.9% and 37.6%, respectively. Table 1 shows the demographic characteristics of all participants with T1DM and T2DM. Results showed that participants with T1DM and T2DM were significantly different in terms of gender (*P* = 0.022), age (*P* < 0.0001), marital status (*P* < 0.0001), job (*P* < 0.0001), BMI (*P* < 0.0001), other chronic diseases (*P* < 0.0001), treatment type (*P* < 0.0001), complications (*P* = 0.001), FBS (*P* = 0.041), and Blood sugar 2-hr postprandial (BS2hpp) (*P* < 0.0001).

Of the 266 enrolled patients, seven with T1DM were excluded due to incomplete questionnaires, and the remaining 259 patients were considered. Table 2 shows that based on the BQ, 38.6% of all participants were at high risk and 61.4% were at low risk for OSA. Results showed that high-risk patients had higher BMI than low-risk ones (29.21 ± 5.46 versus 25.19 ± 4.52). The mean HbA1c of patients in the high-risk group of BQ was 8.01 ± 2.34, and the low-risk group was 7.73 ± 2.41. Comparing low-risk and high-risk participants based on BQ showed a significant difference in age, BMI, neck size, chronic diseases, types of DM, SBQ status, SBQ risk, and use of insulin in these patients (all *P* values less than 0.05).

Table 3 shows that based on the SBQ, 32.8% and 12.3% were at moderate and high risks, respectively. Results showed a significant difference between low and moderate to severe groups regarding sex, age, BMI, neck size, other chronic diseases, types of DM, use of Insulin, Berlin questionnaire, FBS, and HbA1c. Although there was a

Table 1: Demographic characteristics and laboratory results in patients with T1DM and T2DM

Parameters	Total (n=266)	T1DM (n=107)	T2DM (n=159)	<i>P</i>
Sex (male), <i>n</i> (%)	92 (34.6)	28 (26.4)	64 (40.1)	0.022 ^a
Age (year), mean±SD	47.00±19.04	28.55±11.49	59.11±11.78	<0.0001 ^b
Marital status (married), <i>n</i> (%)	182 (71.4)	39 (36.4)	143 (90.0)	<0.0001 ^a
Education, <i>n</i> (%)				
Less than diploma	59 (23.1)	17 (16.0)	42 (28.1)	0.066 ^a
Diploma and Bachelor	150 (58.8)	67 (63.2)	83 (56.8)	
Postgraduate	46 (18.0)	23 (20.8)	23 (15.1)	
Job, <i>n</i> (%)				
Unemployed	17 (6.5)	13 (12.3)	4 (2.6)	<0.0001 ^a
Employed or retired	138 (52.7)	40 (36.8)	98 (63.4)	
Housekeeper	67 (25.6)	15 (14.2)	52 (33.3)	
Student	40 (15.3)	39 (36.8)	1 (0.7)	
BMI (kg/m ²), mean±SD	26.55±5.37	23.76±4.06	28.33±5.26	<0.0001 ^b
Other chronic diseases (yes), <i>n</i> (%)	134 (50.8)	30 (27.4)	104 (66.5)	<0.0001 ^a
The duration of DM (year), mean±SD	12.58±8.40	13.26±8.04	11.89±8.47	0.194 ^b
Treatment type (insulin), <i>n</i> (%)	147 (55.3)	105 (98.1)	42 (26.1)	<0.0001 ^a
Complications (yes), <i>n</i> (%)	80 (30.1)	20 (17.9)	60 (37.6)	0.001 ^a
HbA1c (mg/dl), mean±SD	7.64±1.54	7.74±1.50	7.43±1.97	0.190 ^b
FBS (mg/dl), mean±SD	144.47±55.52	136.04±50.61	149.15±57.56	0.061 ^b
BS2hpp (mg/dl), mean±SD	188.26±71.75	163.48±59.40	203.32±73.70	

^aChi-squared test; ^b independent *t*-test; BMI: Body mass index, HbA1c: Glycosylated hemoglobin, FBS: Fasting blood sugar, BS2hpp: Blood sugar 2-hr postprandial

Table 2: The comparison between low- and high-risk groups based on BQ

Variables	Low-Risk Group	High-Risk Group	P
Sex, n (%)			
Female	111 (69.8)	58 (58)	0.052
Male	48 (30.2)	42 (42)	
Age (years), mean±SD	40.71±16.89	59.45±14.46	<0.001
Diseases, n (%)			<0.001
No disease	97 (61.4)	28 (28.3)	
Other chronic diseases	61 (38.6)	71 (71.7)	
BMI (kg/m ²), mean±SD	25.19±4.52	29.21±5.46	<0.001
Neck size, n (%)			0.086
Less than 40 cm	129 (81.1)	72 (72)	
More than 40 cm	30 (18.9)	28 (28)	
Types of DM, n (%)			<0.001
T1DM	89 (56)	11 (11)	
T2DM	70 (44)	89 (89)	
SBQ status, mean±SD			<0.001
Low risk	126 (79.2)	16 (16)	
Moderate risk	33 (20.8)	52 (52)	
Severe risk	0	32 (32)	
SBQ risk, mean±SD			<0.001
Low risk	126 (79.2)	16 (16)	
Moderate-to-severe-Risk	33 (20.8)	84 (84)	
Medications, mean±SD			<0.001
oral agent	52 (32.7)	67 (67)	
Insulin	107 (67.3)	33 (33)	
FBS, mean±SD	139.83±52.25	152.27±60.37	0.780
HbA1c, mean±SD	7.73±2.41	8.01±2.34	0.779
HbA1c status, mean±SD			0.321
Poor control	79 (49.7)	42 (43.3)	
Good control	80 (50.3)	55 (56.7)	

significant difference between groups regarding quantitative HbA1c, no significant relation was observed between groups regarding HbA1c status.

The mean HbA1c of T1DM and T2DM patients was 7.74 ± 1.50 and 7.43 ± 1.97 , respectively, and did not differ significantly between the two groups. Comparing patients with T1DM and T2DM showed that the frequency of OSA was considerably higher in patients with T2DM based on both questionnaires. Based on BQ results, 56% of T2DM and 11% of T1DM patients had a high risk of developing OSA; and according to SBQ results, 64.1% of T2DM and 15% of T1DM patients had a moderate-to-severe risk of developing OSA.

Discussion

DM is one of the most prevalent chronic disorders worldwide. It has an increased frequency of acute and chronic complications. Among its probable complications, sleep disorders—specifically OSA—have been less noticed.^[3] It is assumed that OSA hurts DM outcomes and IR, resulting in poor glycemic control and more chronic

complications.^[22,23] Although the prevalence of OSA in T2DM and its effect on DM control was repeated in several previous studies,^[24–28] only a few of them evaluated T1DM^[23] or compared T1DM and T2DM.^[29–31]

According to the BQ, 37.3% of all participants were at high risk of OSA and based on the SBQ, 32.8% and 12.3% were at high and moderate risks, respectively. The mean HbA1c of T1DM and T2DM was 7.74 ± 1.50 and 7.43 ± 1.97 , respectively. Besides, comparing patients with T1DM and T2DM showed that the frequency of OSA, according to both questionnaires, was significantly higher in patients with T2DM. Based on BQ results, 56% of T2DM and 11% of T1DM patients had an increased risk of developing OSA. The frequency of high risk of OSA among T1DM and T2DM was consistent with other studies using subjective instruments like BQ to evaluate the frequency of OSA. Keskin *et al.*^[32] reported 50.2% OSA in T2DM, and van Dijk *et al.*^[33] reported 17.2% OSA in T1DM. But it was inconsistent with the results reported by other studies that used objective instruments like polysomnography to determine the prevalence of OSA. Most reported a higher prevalence of OSA in T2DM^[24,27,28,34,35] and T1DM.^[23,36,37]

Based on the SBQ, our results indicated a significant relationship between OSA and glycemic control according in terms of mean HbA1c. This significant association between OSA and HbA1c levels in patients with T2DM was inconsistent with the results of Lam *et al.*^[38] and Ioja *et al.*^[31] Still, it was consistent with the results of Keskin *et al.*^[32]

Furthermore, the significant association in patients with T1DM was inconsistent with the results of Manin *et al.*^[23] and Borel *et al.*^[39] Still, it was consistent with the results of Reutrakul *et al.*^[36]

In our recently published study, we evaluated the detailed reasons behind poor sleep quality affecting glycemic control. Among them, respiratory problems such as coughing or snoring loudly had a significant relationship with higher HbA1C.^[14] This finding is consistent with the current study.

It seems that the significant association between OSA and mean HbA1c based on the SBQ questionnaire and the lack of this association in HbA1c status occurred because the means of HbA1c in both high-risk and low-risk groups of OSA were almost in the good control area. Besides, it may have happened due to the socioeconomic status and a higher level of education of the participants. In this study, the questionnaires were completed online during the COVID-19 pandemic. Therefore, different results may be obtained if the study is repeated with a diverse population regarding social status and uncontrolled blood sugar.

The relationship between OSA and FBS was significant in the SBQ, but there was no statistical significance according to the BQ. The mean FBS differed between high-risk and

Table 3: The comparison between low- and high-risk groups based on SBQ

Variables	Low-Risk Group	Moderate-to-Severe-Risk Group	P
Sex, n (%)			
Female	116 (81.7)	53 (45.3)	<0.001
Male	26 (18.3)	64 (54.7)	
Age (years), mean±SD	38.74±16.43	59.12±13.96	<0.001
Diseases, n (%)			<0.001
No disease	93 (65.5)	32 (27.8)	
Other chronic diseases	49 (34.5)	83 (72.2)	
BMI (kg/m ²), mean±SD	24.81±4.35	29.08±5.37	<0.001
Neck size, n (%)			<0.001
Less than 40 cm	129 (90.8)	72 (61.5)	
More than 40 cm	13 (9.2)	45 (38.5)	
Types of DM, n (%)			<0.001
T1DM	85 (59.9)	15 (12.8)	
T2DM	57 (40.1)	102 (87.2)	
BQ status, mean±SD			<0.001
Low risk	126 (88.7)	33 (28.2)	
High risk	16 (11.3)	84 (71.8)	
Medications, mean±SD			<0.001
Oral agent	44 (31)	75 (64.1)	
Insulin	98 (69)	42 (35.9)	
FBS, mean±SD	137.20±49.47	153.81±61.63	0.019
HbA1c, mean±SD	7.48±1.52	7.89±1.74	0.046
HbA1c status, mean±SD			0.110
Poor control	73 (51.8)	48 (41.7)	
Good control	68 (48.2)	67 (58.3)	

low-risk groups of OSA, and this relationship was not statistically significant. Still, clinically, all of these issues suggested a link between OSA and FBS.

The difference in the results of the two questionnaires in terms of FBS and mean HbA1C can be due to the continuity and the discrete scores and the difference in the type of statistical analysis in BQ and SBQ. It seems that using both questionnaires in the evaluation of OSA was recommended.

It is noteworthy that there was a significant relationship between the risk of OSA according to both questionnaires with age, BMI, other chronic diseases, and the use of insulin. Also, most patients with T1DM had a lower risk of OSA, and T2DM patients had a higher risk of OSA, which may be related to BMI and insulin therapy. As Hanefeld *et al.*^[40] noted, it is assumed that insulin therapy in patients with DM had better results than oral therapies. The role of diabetes and control of OSA is two-sided. It seems that management of OSA can affect the prognosis of diabetes and even the effectiveness of drugs.

On the other hand, the control of diabetes can decrease OSA. Therefore, caregivers should consider OSA, besides other known factors in patients with DM, to access better management of glycemic control in diabetic patients. As the effect of BMI and other chronic diseases on the risk of OSA is demonstrated and perhaps by lowering the BMI and better controlling the other chronic diseases besides

diabetes, we can decrease the risk of OSA and consequently achieve better glycemic control.

Conclusions

Our study showed a significantly higher OSA percentage in T2DM rather than T1DM patients. There was also an association between moderate-to-severe risk of OSA based on the SBQ with mean HbA1c and FBS. Therefore, by controlling the OSA, we may find a way to achieve better glycemic control in diabetic patients.

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Conflicts of interest

There are no conflicts of interest.

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