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Screening Patients with Type 2 Diabetes at High Risk of Obstructive Sleep Apnea: A Single Tertiary Center Experience

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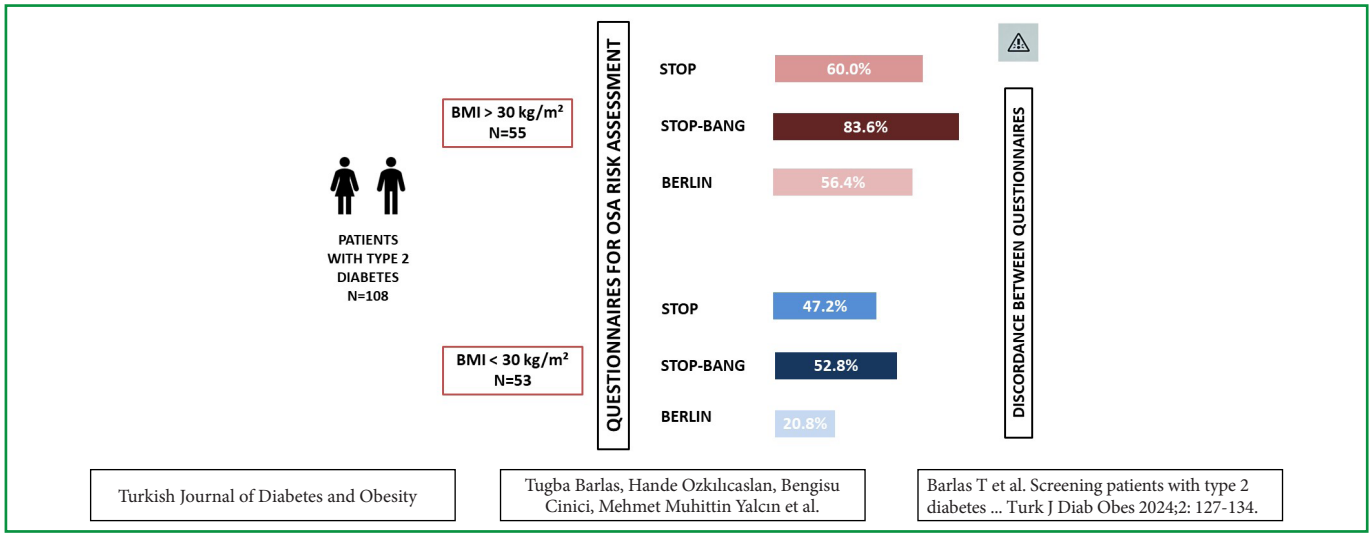
GRAPHICAL ABSTRACT



ABSTRACT

Aim: Current guidelines suggest screening patients with type 2 diabetes (T2D) for obstructive sleep apnea (OSA). However, there is no consensus regarding the optimal method for OSA risk assessment. We aimed to identify those with diabetes who are at high risk for OSA in a tertiary single center and investigate the concordance among questionnaires utilized in assessing high OSA risk.

Material and Methods: STOP, STOP-BANG, and Berlin questionnaires for the assessment of the risk of OSA and the Epworth Sleepiness Scale (ESS) for an investigation of daytime sleepiness were utilized. McNemar test evaluated the agreement between questionnaires. A multivariate logistic regression analysis identified factors influencing high OSA risk.

Results: We included 108 patients, with a median HbA1c of 7.5%, a BMI of 30.7 kg/m², and waist and neck circumferences measuring 104.3 cm and 38.9 cm, respectively. On ESS, 10.2% of patients had excessive daytime sleepiness. According to Berlin (38.9%), the number of patients at high risk of OSA was found to be lower than that of in STOP (53.7%) and STOP-BANG (68.5%) questionnaires. For patients with a BMI<30 kg/m², insufficient consistency was observed between Berlin with STOP and STOP-BANG, whereas there was a

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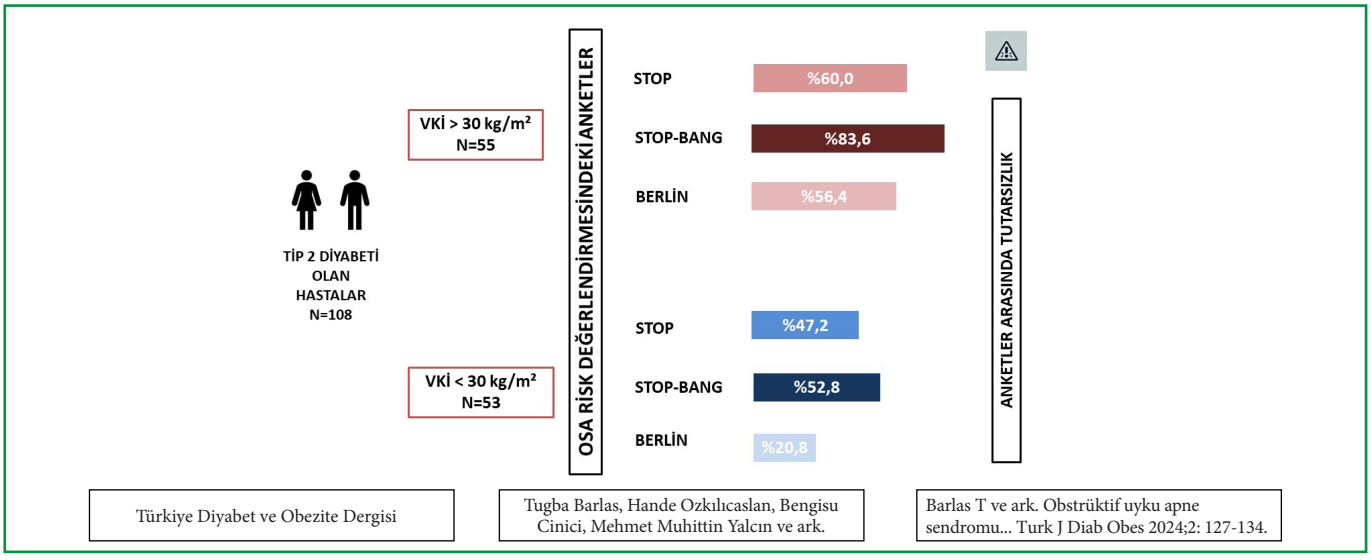
concordance between STOP and STOP-BANG (p<0.05, p=0.453). In those with BMI>30 kg/m², while Berlin and STOP were consistent, no concordance was detected between Berlin and STOP-BANG, as well as between STOP and STOP-BANG (p=0.824, p<0.05). The insulin therapy was the associated factor with a high OSA risk in multivariate logistic regression analysis (p=0.041).

Conclusion: The questionnaires used to predict the risk of OSA in T2D exhibit insufficient compatibility. Insulin therapy contributes to the increased risk of OSA in individuals diagnosed with T2D.

Keywords: *Berlin questionnaire, Epworth Sleepiness Scale, STOP-BANG, Obesity, Type 2 diabetes*

Obstrüktif Uyku Apne Sendromu İçin Yüksek Riskli Olan Tip 2 Diyabet Hastalarının Belirlenmesi

GRAFİKSEL ÖZET



ÖZ

Amaç: Mevcut kılavuzlar, tip 2 diyabet (T2D) hastalarının obstrüktif uyku apnesi (OSA) açısından taranmasını önermektedir. Ancak, OSA risk değerlendirmesi için en uygun yöntem konusunda bir fikir birliği yoktur. Üçüncü basamak bir merkezde, OSA riski yüksek olan diyabet hastalarını belirlemeyi ve yüksek OSA riski değerlendirmesinde kullanılan anketler arasındaki uyumu araştırmayı amaçladık.

Gereç ve Yöntemler: OSA riski değerlendirmesi için STOP, STOP-BANG ve Berlin anketleri ve gündüz uykululuğunu araştırmak için Epworth Uykululuk Ölçeği (ESS) kullanıldı. McNemar testi ile anketler arasındaki uyum, çok değişkenli lojistik regresyon analizi ile yüksek OSA riskini etkileyen faktörler belirlendi.

Bulgular: Çalışmaya dahil edilen 108 hastanın ortanca HbA1c değeri %7,5, vücut kütle indeksi (VKİ) değeri 30,7 kg/m² ve bel ve boyun çevreleri sırasıyla 104,3 cm ve 38,9 cm olarak bulundu. ESS'ye göre hastaların %10,2'sinde aşırı gündüz uykululuğu vardı. Berlin anketine göre (%38,9), yüksek OSA riski taşıyan hasta sayısı, STOP (%53,7) ve STOP-BANG (%68,5) anketlerine göre daha düşük bulundu. VKİ<30 kg/m² olan hastalarda, Berlin ile STOP ve STOP-BANG arasında yetersiz tutarlılık gözlenirken, STOP ile STOP-BANG arasında yeterli uyum vardı (p<0,05, p=0,453). VKİ>30 kg/m² olan hastalarda ise Berlin ile STOP arasında tutarlılık gözlenirken, Berlin ile STOP-BANG ve STOP ile STOP-BANG arasında uyum tespit edilmedi (p=0,824, p<0,05). Çok değişkenli lojistik regresyon analizinde, insülin tedavisinin yüksek OSA riski ile ilişkili faktör olduğu bulundu (p=0,041).

Sonuç: T2D'de OSA riskini tahmin etmek için kullanılan anketler yetersiz uyum sergilemektedir. İnsülin tedavisi, T2D tanısı alan bireylerde artmış OSA riski ile ilişkilidir.

Anahtar Sözcükler: *Berlin anketi, Epworth uykululuk ölçeği, STOP-BANG, Obezite, Tip 2 diyabet*

INTRODUCTION

Obstructive sleep apnea (OSA) is a chronic disease that is identified by recurring instances of either complete (apnea) or partial (hypopnea) obstruction of the upper respiratory tract (1). OSA can lead to elevated levels of carbon dioxide, intermittent deoxygenation, and disrupted sleep patterns. Consequently, there may be a development of sympathetic neuronal activation, resulting in alterations beta cell function (2). Although population-based studies indicate varying rates of OSA incidence, there are studies reporting remarkable rates changing between 23-46% (1, 3). The frequency of OSA is known to rise with increasing obesity, and it serves as a contributory factor for metabolic, cardiovascular, and neurocognitive disorders (4).

The prevalence of type 2 diabetes (T2D) is globally on rise, similar to OSA. Regarding the International Diabetes Federation (IDF) reports, the worldwide prevalence of T2D in individuals aged 20–79 was approximated to be 12.2% (783.2 million) by 2045 (5). Although obesity and age commonly underlie both OSA and T2D, mounting evidence indicates that the connection between these conditions is not solely reliant on obesity (2). It was demonstrated in animal models that intermittent hypoxia leads to a worsening of insulin resistance. Intermittent hypoxia during OSA episodes may directly affect cellular metabolism and contribute to oxidative stress, impacting insulin signaling pathways (6, 7). Furthermore, the sympathetic nervous system could be stimulated by intermittent hypoxia and arousal, leading to an increase in the secretion of stress hormones like cortisol and adrenaline. Elevated levels of these hormones might contribute to poor glycemic control in T2D (2, 8). Moreover, OSA is related with a chronic inflammatory state, which might impair the function of β-cells in the pancreas (7). However, multiple studies have shown that diabetes impacts the regulation of breathing in the central respiratory system and is therefore believed to contribute to the development of OSA (8). The underlying pathophysiology linking T2D and OSA is still under investigation.

Current guidelines indicate that 24–86% of individuals with T2D have OSA, and these guidelines also suggest screening patients with T2D for OSA especially in recent years (9, 10). It was emphasized that screening should be considered for individuals who exhibit symptoms consistent with OSA, like excessive daytime sleepiness, snoring, and witnessed apnea (11). However, in routine practice, aforementioned symptoms might be subjective and there is no clear consensus regarding the optimal method for OSA risk assessment in T2D patients. Polysomnography is the gold standard diagnostic procedure in the evaluation of OSA. However it is time-consuming and costly (12). Herein, we aimed to identify the high-risk patient group for OSA in patients with T2D followed in our center and to investigate the concordance of questionnaires that are used for the evaluation of high OSA risk.

MATERIALS and METHODS

Study Design and Patients

This single-center study was conducted at the endocrinology and metabolism outpatient clinic of a tertiary hospital between July 2023 and September 2023. It has a descriptive, cross-sectional design. Patients with T2D were included according to the following criteria: (i) ≥18 years of age; (ii) followed at our center for at least 1 year; and (iii) treated with insulin and/or oral antidiabetic (OAD) medications. The exclusion criteria comprised the following: (i) diabetes types other than T2D; (ii) pregnancy; (iii) use of any medication associated with sleep disorders; (iv) known diagnosis of OSA or any condition causing airway obstruction; (v) presence of severe co-morbidities such as pulmonary diseases, renal failure or acute heart failure; (vii) psychiatric disorder and related drug usage; (viii) individuals working night shifts. The study adhered to the principles of the Declaration of Helsinki and received approval from the Ethical Board of Gazi University (decision number: 481, date: 05 June 2023). All participants provided written informed consent.

Data Collection

Diabetes mellitus was diagnosed according to the criteria of the American Diabetes Association (13). Demographic features, diabetes-related information, laboratory results and body mass index (BMI), waist and neck circumferences of the patients were documented retrospectively from hospital records. Nephropathy presence was assessed through 24-hour or spot urinalysis (14). Retinopathy, determined through fundus examination, or neuropathy, assessed by examination with a monofilament within the last year, were recorded (15). The presence of cerebrovascular disease, peripheral artery disease, or coronary heart disease was documented as macrovascular complications of T2D (16, 17).

Questionnaires

The Turkish validated versions of STOP, STOP-BANG, and Berlin questionnaires (BQ) were utilized for the evaluation of the risk of OSA in T2D patients (18, 19). The STOP questionnaire consists of four yes-or-no questions regarding: 1. Snoring; 2. Feeling tired, fatigued, or sleepy during the daytime; 3. Observed apnea; and 4. Blood pressure. Two or more "yes" responses indicate a high OSA risk (20). The STOP-BANG questionnaire expands upon the STOP questionnaire by including four additional questions: 1. BMI; 2.

age; 3. neck circumference; and 4. gender. If a patient answers "yes" to three or more items across both sets of questions, it suggests a high risk of OSA (21). The BQ consists of ten questions in three categories: fatigue, hypertension, and snoring (22). In accordance with the scoring criteria, if two or more categories were positive, it signified that patients were at a high OSA risk, whereas having less than two positive categories suggested that patients were at a low risk of OSA.

The Turkish validated version of Epworth Sleepiness Scale (ESS) was also used for an accurate assessment of daytime sleepiness, which is a common question in all three questionnaires (23). The ESS consists eight questions that inquire about the probability of patients falling asleep in typical situations. Widely utilized in clinical and research settings, an ESS score of 11 or higher is generally regarded as excess daytime sleepiness (24).

Statistical Analysis

The IBM SPSS (Version 23.0) statistical software was utilized for statistical analyses. The Shapiro-Wilk test was applied to assess the normal distribution of continuous data. The data were given as mean ± standard deviation (SD), median and interquartile range. Continuous variable comparisons utilized Mann–Whitney U and independent sample t tests, while categorical variables were compared using $\chi 2$ (chi-squared) and Fisher's exact test. Cronbach's alpha coefficient was used to assess the correlation of scores for each item. McNemar test evaluated the agreement between questionnaires. A multivariate logistic regression analysis identified factors influencing high OSA risk. A significance threshold of $p<0.05$ was utilized to determine statistical significance.

The sample size was calculated as 108 at 95% power, 0.32 effect size, and a 0.05 error level using the G*Power 3.1.10 program.

RESULTS

One-hundred eight patients were enrolled. Seventy-two (66.7%) patients were female, and the mean age was 60.8±10.1 years. There were 67 (62%) patients with bed partners. While the median diabetes duration was 10 (7–15) years, the median HbA1c value was 7.5% (6.6–8.9). Anthropometric measurements and the diabetes-related features of the patients are shown in Table 1.

Fifty-five (50.9%) patients had a BMI exceeding 30 kg/m², while 53 patients (49.1%) had a BMI below 30 kg/m². The median BQ score of the patients was 1 (1-2), the STOP score was 2 (1-2), the STOP-BANG score was 3 (2-4), and the ESS score was 3 (1-6). Cronbach's alpha coefficient was 0.84 for the BQ, 0.68 for the STOP, and 0.77 for the STOP-BANG. Figure 1 presents the patients experiencing daytime sleepiness based on the ESS. Patients with T2D are at high risk of OSA, regarding the questionnaires shown in Figure 2. According to the BQ, the number of patients at high risk of OSA was detected to be lower than in STOP and STOP-BANG. For patients with T2D with a BMI below 30 kg/m², although there was concordance between STOP and STOP-BANG ($p=0.453$), sufficient agreement was not observed between BQ and STOP as well as between BQ and STOP-BANG ($p<0.05$). In those with a BMI exceeding 30 kg/m², while concordance was observed between BQ and STOP ($p=0.824$), no agreement was detected between BQ and STOP-BANG, as well as STOP and STOP-BANG ($p<0.05$).

Table 1: Anthropometric measurements and the diabetes-related features of the patients.

Characteristics	Patients with T2D (n=108)
BMI (kg/m²±SD)	30.7 ± 5.7
Waist circumference, (cm±SD)	104.3 ± 13.0
Neck circumference, (cm±SD)	38.9 ± 3.7
Treatment	
Insulin + OAD, n (%)	43 (39.8)
OAD, n (%)	89 (82.4)
Hypertension, n (%)	62 (57.4)
Microvascular complications	
Neuropathy, n (%)	34 (31.5)
Nephropathy, n (%)	10 (9.3)
Retinopathy, n (%)	16 (14.8)
Macrovascular complications	
Coronary artery disease, n (%)	21 (19.4)
Cerebrovascular disease, n (%)	4 (3.7)
Peripheral artery disease, n (%)	18 (16.7)

T2D: Type 2 diabetes, **BMI:** Body mass index, **OAD:** Oral antidiabetics

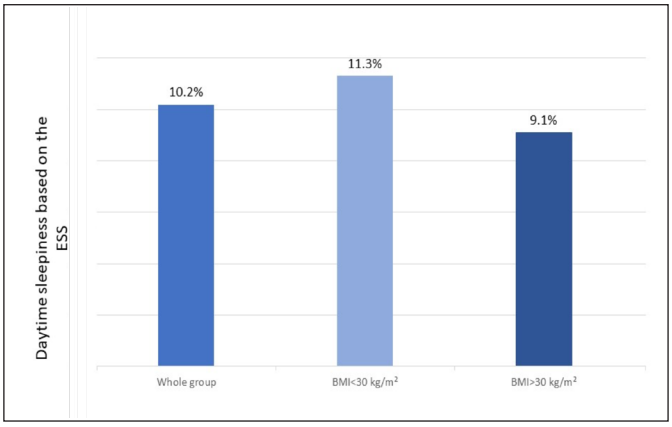


Figure 1: Patients experiencing daytime sleepiness based on the Epworth Sleepiness Scale.

***ESS:** Epworth Sleepiness Scale, **BMI:** Body mass index.*

Table 2: Characteristic features of T2D patients with a high risk of OSA according to all BQ, STOP, and STOP-BANG questionnaires.

Characteristic features of T2D patients	High risk of OSA (n=32)	Not high risk of OSA (n=76)	p value
Male gender, n (%)	9 (28.1)	27 (35.5)	0.456
Age, years	61.6±9.6	60.4±10.3	0.928
Duration of diabetes, years	11.5 (6.2-19.5)	10.0 (7.0-15.0)	0.287
Hypertension, n (%)	25 (78.1)	37 (48.7)	**0.006**
HbA1c, n (%)	8.2 (7.3-10.2)	7.1 (6.5-8.6)	0.091
Insulin therapy, n (%)	19 (59.4)	24 (31.6)	**0.008**
BMI kg/m²	34 (28-39)	29 (26-32)	**0.001**
Waist circumference, cm	111 (100-120)	102 (93-110)	**0.001**
Neck circumference, cm	40.0 (38.0-42.0)	39.0 (36.0-40.7)	0.056
Retinopathy, n (%)	9 (28.1)	7 (9.2)	**0.012**
Neuropathy, n (%)	14 (43.8)	20 (26.3)	0.075
Nephropathy, n (%)	4 (12.5)	6 (7.9)	0.318
Coronary artery disease, n (%)	10 (31.3)	11 (14.5)	**0.044**
Cerebrovascular disease, n (%)	0 (0)	4 (5.3)	0.316
Peripheral artery disease, n (%)	8 (25.0)	10 (13.2)	0.132

T2D: Type 2 diabetes, **OSA:** Obsructive sleep apnea, **BQ:** Berlin questionnaire, **BMI:** Body mass index. Statistically significant values are given in bold

Table 3: Univariate and multivariate logistic regression analysis based on high OSA risk of patients with T2D according to the questionnaires.

Parameters High risk of OSA	Univariate logistic regression			Multivariate logistic regression		
	B coef.	%95 CI	p value	B coef.	%95 CI	p value
Hypertension	1.30	1.41-9.50	**0.007**	0.60	0.61-5.48	0.281
Insulin therapy	1.13	1.31-7.31	**0.009**	0.98	1.03-6.94	**0.041**
Waist circumference	-0.06	0.90-0.97	**0.002**	-0.04	0.91-1.00	0.063
Retinopathy	1.35	1.29-11.52	**0.016**	0.24	0.35-4.61	0.706
Coronary artery disease	0.98	1.00-7.18	**0.049**	0.78	0.68-7.01	0.183
BMI > 30 kg/m²	1.05	1.19-6.87	**0.018**	0.27	0.42-4.05	0.635

OSA: Obstructive sleep apnea, **T2D:** Type 2 diabetes, **BMI:** Body mass index. Statistically significant values are given in bold.

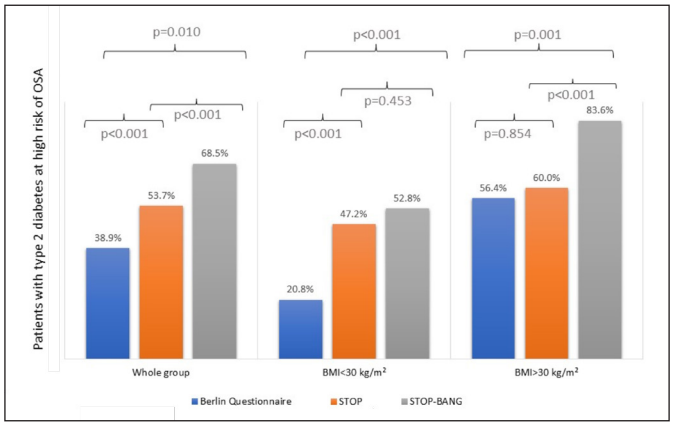


Figure 2: Patients with type 2 diabetes at high risk of obstructive sleep apnea according to questionnaires.

OSA: *Obstructive sleep apnea. McNemar test evaluated the agreement between questionnaires. p<0.05 was accepted as statistical significant.*

When patients with a high risk of OSA were evaluated according to all three questionnaires, the presence of hypertension, insulin therapy, BMI, waist circumference, the presence of retinopathy, and coronary artery disease were detected to be related with a high risk of OSA (Table 2). We observed no gender-related difference regarding a high risk of OSA in our study. Even though the median HbA1c value of high OSA risk group was higher, no statistically significant difference was observed between the two groups. The presence of insulin therapy was the most associated factor with a high OSA risk in logistic regression analysis (Table 3).

DISCUSSION

In our study, the considerable proportion of patients with T2D revealed an elevated risk of OSA. However, it was determined that the questionnaires used to predict the risk of

OSA yielded varying OSA incidences, resulting in inconsistency between them. Although there are conflicting results in studies conducted to investigate the superiority of these questionnaires to each other in patient populations without T2D, it is often reported that the sensitivity of the STOP-BANG questionnaire is slightly higher (25-27). However, there are also studies reporting that these questionnaires are suboptimal for individuals with T2D (28, 29). Westlake et al. emphasized that the sensitivity of the STOP-BANG questionnaire is significantly lower in women compared to men with T2D (28). Based on our findings and existing literature, it is essential to develop more sensitive screening tests to identify patients at high risk for OSA. This approach can help prioritize which patients with T2D should undergo more time-consuming and costly tests like polysomnography.

Depending on the questionnaire utilized, our study indicated that patients with T2D had a high risk of OSA, with prevalence rates varying between 39-68%. In some studies conducted on patients with T2D, the high risk of OSA with BQ was found to be ranging from 42-44% (30, 31). In another screening study utilizing the STOP-BANG questionnaire, the high risk of OSA among individuals with T2D was determined to be 63% (32). In a study involving 58 patients with T2D, where both questionnaires were administered to the same patient group, a high risk of OSA was identified in 74% based on the BQ and 62% using the STOP-BANG questionnaire (33). These differences reveal that the method used in screening for OSA is highly important.

As expected and in accordance with the established literature (34, 35), our study revealed an association between an elevated risk of OSA and elevated BMI, increased waist circumference, hypertension, and coronary artery disease. The prevalence of OSA can reach levels ranging from 40% to 80% in individuals with co-morbidities (36). OSA and T2DM is known to share common pathophysiological mechanisms related to the cardiovascular complications in particular (37). Hence, detecting and treating OSA will be beneficial to prevent this synergistic effect.

Even though the T2D patients at a high risk of OSA exhibited a greater BMI compared to those at low risk, insulin therapy emerged as the most associated factor when considering the collective analysis of risk-increasing factors for OSA. This data strenghten the perspective that factors beyond obesity play a role in the increased risk of OSA in patients with T2D. Consistent with our results, in a population-based study, it was reported that, following adjustments for BMI, individuals with diabetes treated with insulin therapy had a 43% higher OSA risk (38).

Despite a higher neck circumference in the high OSA risk group compared to the low OSA risk group, no statistically significant difference was observed in our study. While some studies in the literature suggest that neck circumference serves as an independent predictor of high-risk OSA (34, 35), there are also studies similar to our findings that did not identify a significant association (30). This might be attributed to factors such as the sample size, as well as potential influences from gender and anatomical variations among the patients.

Our study had some limitations. First of all, the assessment of OSA risk was conducted using questionnaires, and the survey data were not validated through polysomnography, which serves as a definitive diagnostic method. However, it is important to note that the questionnaires used in the study have been validated and extensively utilized in both clinical settings and research studies. In addition, because of the cross-sectional design of the study, cause-and-effect relations among the variables could not be determined.

Our results indicate that the questionnaires used to predict the OSA risk in individuals with T2D exhibit insufficient compatibility. Considering that polysomnography is time-consuming and costly, it is important in clinical practice to correctly select high-risk patients and a more comprehensive screening approach is essential for assessing the risk of OSA in T2D.

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Authors Contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by **Tugba Barlas, Hande Ozkilicaslan, Bengisu Cinici, Mehmet Muhittin Yalcin, Mujde Akturk, Fusun Balos Toruner, Ayhan Karakoc** and **Alev Eroglu Altinova.** The first draft of the manuscript was written by **Tugba Barlas, Alev Eroglu Altinova** and **all authors** commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflict of interest
The authors declare that they have no conflict of interest in relation with the present study.

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Ethics approval
The study was approved by Gazi University Ethical Board.

Availability of data and material
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Peer Review Process
Extrmely and externally peer-reviwed.

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