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Relationship Between Hemoglobin Glycation and AHI Index in Patients With Non-diabetic OSAS

ABSTRACT

Aim: Type 2 diabetes mellitus (T2DM) is one of the most common comorbidities in patients diagnosed with obstructive sleep apnea syndrome (OSAS). The Hemoglobin Glycation Index (HGI) has been introduced as a new index of glycation, instead of HbA1c. We aimed to evaluate the relationship between the disease severity and HGI in non-diabetic patients diagnosed with OSAS, in comparison to diabetic patients.

Methods: Our study included 117 patients with OSAS, of whom 66 were non-diabetic while 51 patients had T2DM.

Results: A difference was observed between the groups in terms of age ($P = .002$), HGI (0.347 ± 0.25 vs. 1.380 ± 1.7; $P < .0001$), predicted HbA1c ($P < .0001$), HbA1c ($P < .0001$), fasting blood glucose ($P < .0001$), eosinophil count ($P = .003$), and total supine time ($P = .044$). The intragroup evaluation of groups 1 and 2 showed no significant relationship between HGI and the severity of OSAS, both in the diabetic and the non-diabetic groups ($P > .05$). The correlation analysis in the DM group showed HGI to be negatively correlated with predicted HbA1c, fasting blood glucose, Hgb, and RBC, but positively correlated with HbA1c, non-REM stage 3, and supine deep sleep time. In the non-DM group, a positive correlation of HGI was found with BMI, HbA1c, total apnea, central apnea, obstructive apnea, total mixed apnea counts, apnea index, total supine sleep time, and supine deep sleep time. However, a negative correlation was found with the non-REM stage 1 ($P < .05$ for all).

Conclusion: HGI is a new glycation index that shows no significant relationship with the severity of the disease or increased AHI, both in the non-diabetic and diabetic OSAS patients.

Keywords: Hemoglobin Glycation Index (HGI), OSAS severity, sleep apnea syndrome (OSAS), type 2 diabetes mellitus (T2DM)

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a common sleep disorder characterized by sleep interruptions and episodes of apnea. It causes intermittent deoxygenation.[1] OSAS has many risk factors such as obesity, hypertension, insulin resistance, and type 2 diabetes mellitus (T2DM).[2] Patients with OSAS have a consequential linkage with TP2DM due to the possibility of recurrent hypoxia, endothelial dysfunction, and insulin resistance. Epidemiological studies have revealed a high prevalence of OSAS in T2DM patients. In a recent study, up to 23% of the diabetic population were found to have OSAS, along with a high prevalence of T2DM or insulin resistance in OSAS patients. A cross-sectional study reported that 30.1% of OSAS patients had T2DM, and a recent meta-analysis showed that moderate to severe OSAS was found associated with an increased incidence of T2DM. Thus, the increased severity of OSAS worsens the control of DM, finally resulting in severe OSAS, which might also accompany the DM-related micro and macrovascular complications.[3] Similarly, the irregularities reported in patients diagnosed with non-diabetic OSAS were due to recurrent hypoxia attacks related to the severity of the disease, which may cause the development of T2DM in the future.[4] HbA1c is an important parameter in the follow-up of diabetic patients. High HbA1c is associated with an increased risk of diabetic micro and macrovascular complications. A study on this subject shows that reducing every unit of HbA1c by approximately 1% results in a decrease of the risk of microvascular events by approximately 25%.[5] Increased severity of OSAS has been found to be significantly

associated with the increased HbA1c levels in diabetic and non-diabetic patients ($P = .04$ for diabetic patients and $P < .05$ for non-diabetic patients).[6-8] Although HbA1c is a universally accepted guide for the follow-up treatment of DM, it has arguable limitations in clinical practice due to inter-individual variations in the propensity for glycation, both in healthy individuals and in diabetic patients.[8] To overcome this arguable limitation, the HGI was introduced as a new index of glycation by Hempe et al.[10] in 2002. The HGI is calculated by subtracting the predicted HbA1c level from the measured HbA1c level. The predicted HbA1c is calculated based on the observed mean blood glucose using a linear regression equation between blood glucose and HbA1c levels. A significant association between the high HGI levels and the risk for diabetic microvascular complications is seen in T1DM and T2DM patients ($P < .05$ in all). In another study, the risk for mortality was found to be significantly higher in the group with high HGI value in T2DM patients ($P < .0001$).[9-11] Moreover, increased HGI in non-diabetic individuals was associated with an impaired metabolic picture and increased cardiovascular complications.[12]

Thus, the relationship between HGI, a risk factor for increased complications in diabetic and non-diabetic patients, and the severity of the disease in OSAS has not been investigated sufficiently in the literature. Therefore, we aimed to investigate the relationship between HGI and OSAS parameters. Previous studies have demonstrated an increase in the parameters of T2DM with increased OSAS severity, while the increased HGI value was associated with the increase in OSAS parameters in the diabetic OSAS group. Therefore, we aimed to evaluate this relationship in non-diabetic patients, which has not been emphasized much previously. Therefore, non-diabetic patients were accepted as the main study group, while the T2DM group was designed as a control group.

METHODS

Study Population

The study sample consisted of 117 adult patients (≥18 years) diagnosed with T2DM but without a prior diagnosis of sleep apnea. They were recruited from an outpatient pulmonology clinic from December 2019 to May 2020. However, we excluded the patients with a diagnosis of T1DM, central type sleep apnea, a history of neurological diseases such as cerebrovascular disease and recent head trauma, along with those who had cardiovascular diseases, including heart failure, acute coronary syndrome, or history of idiopathic pulmonary hypertension. Patients were subjected to overnight polysomnography (PSG) testing and 12-hour fasting-routine biochemistry laboratory examinations, which included parameters of diabetes control (HbA1c, fasting blood glucose, and lipid profiles). Fasting blood glucose, total cholesterol, triglycerides (TG), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) were measured using the routine laboratory methods (with Cobas 8000) (Roche Diagnostics®, Germany) autoanalyzer. HbA1c values were measured with a turbidimetric inhibition immunoassay (Cobas Integra 400 plus) (Roche Diagnostics, Germany). Additionally, demographic characteristics (age, gender, weight, height) were recorded. The patients' complete blood counts, liver function tests, and levels of thyroid-stimulating hormone were found to be within the normal limits.

Polysomnography (PSG)

The diagnosis of OSAS was made by polysomnography (PSG). The overnight examination was conducted (using a Philips Respironics Polysomnography Device, PA, USA; Respironics Deutschland Gewerbestrasse, Herrsching, Germany). Further, four-channel electroencephalogram (EEG), two-channel electrooculography (EOG), submental electromyography (EMG), pulse-oximetry, thoracic and abdominal movements, electrocardiogram (ECG), tracheal sounds, and oronasal airflow were recorded. In PSG, measurements of respiratory decrease (H = hypopnea) and complete stoppage of respiration (A = apnea) were calculated along with the hourly apnea (A)-hypopnea (H) counts (I = index). The stoppage of airflow for more than 10 s was defined as apnea, while a 4% reduction in oxygen saturation and >30% reduction in airflow for more than 10 s were defined as a hypopnea. The scale of severity of OSAS was accepted as mild OSAS if the AHI (apnea-hypopnea index) was 5-15/h; moderate OSAS if the AHI was 16-30/h, and severe OSAS if the AHI was > 30/h. Based on their AHI scores, all patients were grouped as mild (AHI: 5-15), moderate (AHI: 15-30), and severe (AHI> 30) OSAS patients.[13] All PSG recordings were reported on the same day by the same doctor, who was blinded to study protocol.

Calculation of HGI

The concomitant HbA1c and fasting blood glucose (FBG) values of all participants were recorded on the graph to establish a linear relationship. The equation for calculating predicted HbA1c (Pred-HbA1c) was (Pred-HbA1c = 0:008 X FBG + 6:28), as depicted in a previous study.[11] Then, HGI was calculated according to the previous study equation as the difference between the measured HbA1c and the predicted HbA1c.[11]

Reproducibility

In order to calculate the intraobserver and interobserver coefficients of variation in the measurements of the PSG recordings and HGI results, 20 patients were randomly selected among the severe group and assessed by repeating the measurements under the same baseline conditions. To test the interobserver variability, a second observer performed the measurements offline from video recordings. The intraobserver and interobserver coefficients of variation for PSG and HGI measurements were <5% and nonsignificant.

Statistical Analysis

This study was aimed to test the relationships between the group variables of AHI and other variables. Considering the number of observations on a group basis, parametric and non-parametric hypothesis tests were applied for quantitative data. To compare the quantitative medical parameters between the AHI groups, ANOVA and Kruskal–Wallis tests were applied according to the normal distribution of the data. The Shapiro–Wilk test was used to test the normal distribution. For categorical data, the chi-square test was used to test the relationships between AHI groups according to gender. Relationships between normally distributed variables were tested with Pearson Correlation Analysis, and non-normally distributed relationships were tested with Spearman's rho analysis. The findings of statistical data analysis were obtained using the Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA).

RESULTS

Of the 117 patients participating in the study, 66 patients were non-diabetic (56.4%; group 1), and 51 were diabetic (43.5%; group 2). Group 1 had a total of 30 (26%) males and 36 (31%) females, while group 2 had 28 (24%) males and 23 (20%) female patients. In terms of basal characteristics, comparison between the groups showed a difference in terms of age (52 ± 10 vs. 59 ± 10; $P = .002$), HGI (0.347 ± 0.25 vs. 1.380 ± 1.7; $P < .0001$), predicted HbA1c (5.5 ± 0.1 vs. 6.4 ± 0.8; $P < .0001$), HbA1c (5.8 ± 0.3 vs. 7.7 ± 1.7; $P < .0001$), fasting blood glucose (96 ± 14 vs. 150 ± 56; $P < .0001$), and eosinophil count (0.2 ± 0.3 vs. 0.3 ± 0.9; $P = .003$). In terms of sleep test parameters, the difference between the groups was observed in the total supine time (128.4 ± 99.2 vs. 88.4 ± 69.7; $P = .044$) (Table 1). Groups 1 and 2 in themselves were also grouped according to the severity of the disease and their relationship with variables, especially in terms of HGI. Group 2 showed a significant difference in terms of pre albumin, AHI, total sleep time, total apnea, hypopnea, apnea and hypopnea, central apnea, obstructive apnea, mixed type apnea counts, non-REM and REM rates, REM-AHI, apnea index, left-side sleep AHI, right-side sleep AHI, hypopnea index, and supine sleep period AHI. In terms of HGI, there was no significant relationship observed with the severity of OSAS or increased AHI ($P > .05$). Similarly, in group 1, there was no significant relationship between HGI and OSAS severity ($P > .05$). In group 1, a significant difference was observed in terms of AHI, sleep efficiency rate, total apnea, hypopnea, apnea and hypopnea, central apnea, obstructive apnea, mixed type apnea counts, non-REM, non-REM stage 1, REM rates, non-REM-AHI, REM-AHI, apnea and hypopnea index, and the AHI scores of left, right, and supine sleep periods (Table 2). According to correlation analysis, the group diagnosed with DM (group 2) showed significant negative correlation of HGI with predicted HbA1c ($r = -0.377$), fasting blood glucose ($r = -0.377$), Hgb ($r = -0.459$), and RBC ($r = -0.454$) and significant positive correlation with HbA1c ($r = 0.438$), non-REM stage 3 ($r = 0.372$), and deep supine sleep time ($r = 0.455$) (all $P < .05$); in the non-DM group (group 1), positive significant correlations were observed with BMI ($r = 0.239$), HbA1c ($r = 0.719$), total apnea counts ($r = 0.349$), total central apnea counts ($r = 0.245$), total obstructive apnea counts ($r = 0.331$), total mixed apnea counts ($r = 0.289$), apnea index ($r = 0.288$), total supine sleep time ($r = 0.357$), and deep supine sleep time ($r = 0.258$), while negative significant correlations were observed with non-REM stage 1 ($r = -0.351$) (all $P < .05$, Table 3).

DISCUSSION

There is a well-known relationship between sleep disorders and pathophysiological changes, which may cause T2DM. The prevalence of OSAS is high in diabetic patients, and the interruption of sleep with deoxygenation and apnea attacks are known to cause a decrease in insulin sensitivity in the long term. The results of observational studies have reported an increased risk of developing diabetes in such patients and even in patients without diabetes. The presence of OSAS has been reported to cause a 25% increase in insulin resistance.[14] The relationship between OSAS and diabetes is bidirectional, where the incidence of T2DM is related to the severity of OSAS as well. Glycemic control is worse in patients with severe OSAS. Therefore, a positive correlation has been reported between the presence of OSAS and HbA1c ($P = .02$).[15] A cross-sectional study conducted by Rusu et al.[3] involved 100 patients newly diagnosed with T2DM and OSAS. After making corrections for gender, age, diabetes duration and treatment, and BMI (body mass index), HbA1c was determined to be higher in patients with OSAS than in the healthy control group (8.4% vs. 7.6%, respectively; $P = .04$). A positive correlation was found between the presence of OSAS and HbA1c ($r = 0.24$, $P = .02$). Moreover, no significant variation was found in HbA1c levels according to the OSAS severity ($P = .08$). After adjusting for all confounding factors in univariate analysis, the lowest oxygen saturation during sleep remained significantly associated with HbA1c ($P = .05$).[16] Additionally, Siwasaranond et al.[17] found no significant relationship between the AHI and glycemic control in patients with T2DM. Sleep duration was found to be inversely correlated with HbA1c ($r = -0.264$, $P = .026$). After adjusting for the confounding factors, including AHI, the multiple regression analysis showed that only the sleep duration was significantly associated with HbA1c ($P = .005$). A reduction in each hour of sleep duration was associated with a 4.8% increase in HbA1c levels (95% CI:1.5-8.0).[17]

Hemoglobin Glycation Index (HGI)

Although it is clear that the risk of complication of HbA1c is due to diabetes, the differences and variabilities have been revealed in the glycation tendency of each individual, both in healthy individuals and in diabetic patients. To overcome these issues, Hempe developed a mathematical method and defined it as the HGI. HGI is based on the quantitative determination of the difference between the measured HbA1c and predicted HbA1c. The prevalence of microvascular events was higher in the high HGI group (≥0.29 for HGI). A significantly higher risk of major cardiovascular events was also found in the high HGI group compared to the low HGI group (HR 1.26 [95% CI: 1.09-1.46]; $P = .002$). Moreover, the risk for major microvascular events and mortality was also higher in the high HGI group (HR 1.46 [95% CI: 1.26-1.69], $P < .0001$ and HR 1.36 [95% CI: 1.17-1.59], $P < .0001$, respectively).[10] Besides, the high HGI level in non-diabetic patients is associated with fatty liver and is a marker for many cardiovascular and diabetic complications. In the DCCT (Diabetes Control and Complications Trial) study, high HGI level was also found to be associated with an increased risk of retinopathy and nephropathy in the T1DM group.[18] Similarly, in another cross-sectional study involving 1505 non-diabetic patients, a worse metabolic control was determined along with low eGFR levels in the groups with moderate and high HGI levels. After adjusting the confounding factors, subjects in the highest quartile of HGI had an increased risk of CKD compared to the group in the lowest quartile (OR: 3.44; 95% CI: 1.01-12.54, $P = .05$).[19] In the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, increased rates of cardiovascular diseases, stroke, and peripheral artery disease were found to be significantly associated with the group with a high HGI value. In a recent study, it was stated that a high HGI level was associated with increased coronary artery calcification and an increased risk of atherosclerosis in non-diabetic patients. This suggests that HGI may have an additional effect on macrovascular complications, beyond the HbA1c level.[20,21] Thus, HGI is associated with an increased risk of micro and macrovascular complications in diabetic and non-diabetic patients, and may help in predicting the risk.[15]

Table 1. Basal Characteristics and PSG Results with Laboratory Findings

	DM										Comparison of All Groups According to AHI
	None: Group 1					Present: Group 2					
	Count, n = 66 (56.4% in total)					Count, n = 51 (43.5% in total)					
OSAS	Mild (Group a), n = 19 (16.2%); m: 9, f: 10	Moderate (Group b), n = 21 (18%); m: 9, f: 12	Severe (Group c), n = 26 (22.2%); m: 12, f: 14	Total, n = 66 (56.4%); m: 30 (26%), f: 36 (31%)	$P^{\psi,\Omega}$	Mild (Group d), n = 18 (15.3%); m: 10, f: 8	Moderate (Group e), n = 17 (14.5%); m: 8, f: 9v	Severe (Group f), n = 16 (13.6%); m: 10, f: 6	Total, n = 51 (43.5%);m: 28 (24%), f: 23 (20%)	$P^{\psi,\Omega}$	$P^{\mu,¥}$
Age	51 ± 10	51 ± 9	53 ± 11	52 ± 10	NS$^{\psi}$	61 ± 8	60 ± 10	57 ± 11	59 ± 10	NS$^{\psi}$	.002$^{\mu}$
BMI	33 ± 6	33.7 ± 6.8	33.3 ± 5.6	33.3 ± 5.9	NS$^{\psi}$	37 ± 6.9	35 ± 6.5	35.2 ± 3.6	35.5 ± 5.2	NS$^{\psi}$	NS$^{\mu}$
Prealbumin	23 ± 4	24 ± 4	22 ± 5	23 ± 5	NS$^{\psi}$	24 ± 1	19 ± 4	23 ± 3	22 ± 4	.043$^{\Omega}$	NS$^{\mu}$
A/H ratio-index (AHI)	6.9 ± 3.7	21.0 ± 3.7	52 ± 20.1	29.4 ± 25	<.0001$^{\Omega}$	4.4 ± 4.1	22.3 ± 5	57.9 ± 22.4	36.5 ± 27.7	<.0001$^{\Omega}$	NS$^{¥}$
HGI	0.321 ± 0.26	0.339 ± 0.23	0.366 ± 0.28	0.347 ± 0.25	.804$^{\Omega}$	1.422 ± 1.3	1.176 ± 0.9	1.485 ± 2.2	1.380 ± 1.7	NS$^{\Omega}$	<.0001$^{¥}$
Pred-HBA1C	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	5.5 ± 0.1	NS$^{\psi}$	5.8 ± 0.3	6.4 ± 0.4	6.5 ± 1.1	6.4 ± 0.8	NS$^{\Omega}$	<.0001$^{\mu}$
HAB1C	5.8 ± 0.3	5.9 ± 0.3	5.8 ± 0.3	5.8 ± 0.3	NS$^{\psi}$	7.2 ± 1.2	7.6 ± 1.2	8.0 ± 2.1	7.7 ± 1.7	NS$^{\Omega}$	<.0001$^{\mu}$
Glucose	94 ± 12	98 ± 12	97 ± 17	96 ± 14	NS$^{\psi}$	116 ± 23	155 ± 31	161 ± 71	150 ± 56	NS$^{\Omega}$	<.0001$^{\mu}$
Hgb	14.8 ± 1.4	14.4 ± 2.1	14.8 ± 1.7	14.7 ± 1.6	NS$^{\psi}$	14 ± 1.5	14.5 ± 1.8	15.3 ± 1.8	14.8 ± 1.8	NS$^{\psi}$	NS$^{\mu}$
RBC	5.1 ± 0.46	4.9 ± 0.51	5.1 ± 0.6	5.1 ± 0.5	NS$^{\psi}$	4.8 ± 0.5	4.9 ± 0.6	5.2 ± 0.6	5.0 ± 0.6	NS$^{\psi}$	NS$^{\mu}$
WBC	8.63 ± 2.52	7.64 ± 1.91	8.3 ± 2.3	8.3 ± 2.3	NS$^{\Omega}$	8.9 ± 3.2	7.4 ± 1.7	7.9 ± 1.5	7.9 ± 2.0	NS$^{\psi}$	NS$^{\mu}$
Lymphocyte	2.41 ± 0.9	2.5 ± 0.4	2.5 ± 0.9	2.5 ± 0.8	NS$^{\psi}$	2.5 ± 0.6	2.2 ± 0.5	2.5 ± 0.6	2.4 ± 0.6	NS$^{\psi}$	NS$^{\mu}$
Neutrophil	5.1 ± 2.4	4.2 ± 1.6	4.7 ± 1.7	4.8 ± 2.0	NS$^{\psi}$	5.2 ± 2.5	4.3 ± 1.1	4.3 ± 1.5	4.5 ± 1.6	NS$^{\psi}$	NS$^{\mu}$
Platelet	269 ± 57	271 ± 88	258 ± 75.6	267 ± 72	NS$^{\psi}$	236.5 ± 109.9	263.6 ± 50.8	272.5 ± 53.3	263 ± 66	NS$^{\psi}$	NS$^{\mu}$
Monocyte	0.6 ± 0.2	0.5 ± 0.1	0.6 ± 0.1	0.6 ± 0.1	NS$^{\psi}$	0.7 ± 0.2	0.6 ± 0.2	0.6 ± 0.1	0.6 ± 0.2	NS$^{\Omega}$	NS$^{\mu}$
Eosinophil	0.3 ± 0.5	0.3 ± 0.3	0.2 ± 0.1	0.2 ± 0.3	NS$^{\Omega}$	0.1 ± 0.2	0.1 ± 0.1	0.4 ± 1.3	0.3 ± 0.9	NS$^{\Omega}$	.003$^{¥}$
Basophil	0.04 ± 0.02	0.06 ± 0.03	0.05 ± 0.02	0.05 ± 0.03	NS$^{\Omega}$	0.03 ± 0.01	0.04 ± 0.01	0.1 ± 0.2	0.07 ± 0.1	NS$^{\Omega}$	NS$^{¥}$
MVC	86.9 ± 4.3	87.1 ± 5.7	87.2 ± 5.3	87.1 ± 4.9	NS$^{\psi}$	88.7 ± 2.6	88.9 ± 4.1	88 ± 3.0	88.4 ± 3.3	NS$^{\psi}$	NS$^{\mu}$
MCH	28.7 ± 2	29 ± 2.3	28.8 ± 2.1	28.8 ± 2.1	NS$^{\Omega}$	29 ± 1.4	29.2 ± 1.8	29.3 ± 1.4	29.2 ± 1.5	NS$^{\psi}$	NS$^{\mu}$
MCHC	32.8 ± 1.5	33.2 ± 1.1	32.4 ± 3.4	32.8 ± 2.5	NS$^{\Omega}$	32.7 ± 0.8	32.8 ± 1.4	33.3 ± 1.1	33.1 ± 1.2	NS$^{\psi}$	NS$^{\mu}$
RDW	13.6 ± 2	13.7 ± 1.5	13.6 ± 1.2	13.6 ± 1.7	NS$^{\Omega}$	13.2 ± 0.8	13.1 ± 1.0	13.0 ± 1.0	13.1 ± 1.0	NS$^{\Omega}$	NS$^{¥}$
MPW	10.1 ± 0.8	10.5 ± 1.6	9.9 ± 0.9	10.2 ± 1	NS$^{\Omega}$	10.9 ± 1.1	10.4 ± 0.9	10.5 ± 1.0	10.6 ± 1.0	NS$^{\psi}$	NS$^{\mu}$
CRP	0.5 ± 0.3	0.3 ± 0.2	0.7 ± 1.1	0.6 ± 0.8	NS$^{\Omega}$	0.4 ± 0.4	0.7 ± 0.5	0.7 ± 0.8	0.6 ± 0.6	NS$^{\Omega}$	NS$^{¥}$
Creatinine	0.6 ± 0.3	0.6 ± 0.4	0.5 ± 0.1	1.1 ± .06	NS$^{\Omega}$	1 ± 0.5	0.9 ± 0.1	1.0 ± 0.1	1.1 ± 0.5	NS$^{\Omega}$	NS$^{¥}$
Total Cholesterol	202 ± 44.7	186.5 ± 47.7	179.4 ± 37.3	190 ± 43	NS$^{\psi}$	199 ± 27.6	165.3 ± 49.6	193.4 ± 42.3	186 ± 43	NS$^{\psi}$	NS$^{\mu}$
LDL-Cholesterol	123 ± 42.1	107 ± 43.2	107.4 ± 33.6	113 ± 39	NS$^{\psi}$	120.5 ± 25.1	98.6 ± 47.4	110.0 ± 40.7	109 ± 40	NS$^{\psi}$	NS$^{\mu}$
HDL-Cholesterol	47 ± 20	46.1 ± 22.9	47.1 ± 40.9	47 ± 31	NS$^{\Omega}$	45.6 ± 8.6	39 ± 6.2	53.8 ± 39.0	48 ± 28	NS$^{\Omega}$	NS$^{¥}$
Triglyceride	208 ± 84.8	336.3 ± 63.4	171 ± 119.8	194 ± 124	NS$^{\Omega}$	167.6 ± 52.1	140.3 ± 55.4	227.2 ± 126.9	190 ± 103	NS$^{\Omega}$	NS$^{¥}$
Total sleep time	278.8 ± 84.8	336.3 ± 63.4	317.6 ± 87.2	302.2 ± 90.4	NS$^{\Omega}$	216.6 ± 105.7	299.0 ± 60.3	335.3 ± 51.6	300.7 ± 79.4	.036$^{\Omega}$	NS$^{¥}$
Efficiency/Sleep	65.1 ± 20	129.1 ± 194.4	78 ± 15.5	80.5 ± 31.3	.009$^{\Omega}$	67.4 ± 20.2	75.5 ± 13.9	76.9 ± 12.0	74.6 ± 14.4	NS$^{\Omega}$	NS$^{¥}$
Total count of apnea	9.3 ± 11.3	17.8 ± 13.9	104.3 ± 110.3	53 ± 87	<.0001$^{\Omega}$	3 ± 3.3	14.4 ± 10.3	120.2 ± 147.1	65 ± 117	.001$^{\Omega}$	NS$^{¥}$

Total count of hypopnea	23 ± 17.7	99.1 ± 24.2	175.6 ± 83.8	104 ± 91	<.0001[Ω]	16.8 ± 25.2	97.5 ± 34.7	213 ± 99.5	139 ± 108	<.0001[Ω]	NS[¥]
Total count of apnea + hypopnea	32.3 ± 19	117 ± 25.8	279.9 ± 139.5	157 ± 148	<.0001[Ω]	19.8 ± 27.4	112 ± 35.9	333.2 ± 160.1	204 ± 177	<.0001[Ω]	NS[¥]
Total count of central apnea	2.5 ± 3.8	5.3 ± 5	16.1 ± 23.5	9 ± 17	<.0001[Ω]	1.6 ± 2	3.8 ± 4.6	21.9 ± 33.5	12 ± 25	.037[Ω]	NS[¥]
Total count of obstructive apnea	5.2 ± 8.2	9.4 ± 8.4	73.4 ± 85.8	36 ± 66	<.0001[Ω]	0.8 ± 1.3	7.3 ± 6.3	70.2 ± 89.6	37 ± 71	<.0001[Ω]	NS[¥]
Total count of mixed apnea	1.2 ± 2.9	3 ± 3.3	14.7 ± 19.9	8 ± 15	<.0001[Ω]	0.5 ± 0.8	3.2 ± 5.3	28.1 ± 41.8	15 ± 32	.008[Ω]	NS[¥]
Non-REM ratio	95.3 ± 7.1	90.3 ± 6.6	96.6 ± 42	95.1 ± 6.3	.026[Ω]	87.7 ± 6.4	95.9 ± 5.1	94.4 ± 5.4	93.5 ± 6.2	.044[Ω]	NS[¥]
Ratio of non-REM stage 1	18.9 ± 13	13.7 ± 7.2	10.6 ± 9.8	14.4 ± 11.4	.006[Ω]	17.4 ± 11.8	15.7 ± 15.4	16.8 ± 12.8	16.7 ± 13.1	NS[Ω]	NS[¥]
Ratio of non-REM stage 2	52.2 ± 15.1	57 ± 13.8	55.7 ± 16.5	54.6 ± 15.5	NS[Ψ]	48.3 ± 15.0	46.1 ± 11	55.8 ± 12.7	51.4 ± 13.1	NS[Ψ]	NS[µ]
Ratio of non-REM, stage 3	24,2 ± 17,7	19.7 ± 9.9	30.3 ± 20.9	26.2 ± 18.5	NS[Ω]	21.9 ± 12.6	33.9 ± 20.5	21.8 ± 20.7	25.4 ± 19.5	NS[Ω]	NS[¥]
REM ratio	4,6 ± 7,1	9.6 ± 6.6	3.2 ± 4.2	4.8 ± 6.2	.025[Ω]	12.2 ± 6.4	4 ± 5	5.5 ± 5.4	6.4 ± 6.1	.044[Ω]	NS[µ]
Non-REM-AHİ	6.5 ± 3.6	19.9 ± 4.2	50.2 ± 19.7	28.2 ± 24.4	<.0001[Ω]	4.1 ± 3.7	20.7 ± 4.5	96.3 ± 162.9	55.2 ± 120.8	<.0001[Ω]	NS[¥]
REM AHİ	2.5 ± 5.4	23.3 ± 18.9	30.8 ± 33.4	18.6 ± 27.0	<.0001[Ω]	3.1 ± 4.3	10.5 ± 17.7	35.9 ± 26.6	21.7 ± 25.4	.029[Ω]	NS[¥]
Index of apnea	2.0 ± 2.3	3.1 ± 2.4	18.4 ± 16.8	9.5 ± 13.8	<.0001[Ω]	0.7 ± 0.9	3.0 ± 2.4	19.9 ± 22.4	11.0 ± 18.1	.001[Ω]	NS[¥]
Index of hypopnea	5.0 ± 3.7	17.8 ± 3.9	33.4 ± 12.8	19.8 ± 15.8	<.0001[Ω]	3.5 ± 3.7	19.2 ± 4.8	37.9 ± 14.8	25.4 ± 17.5	<.0001[Ψ]	NS[µ]
AHI during left-side sleep	24.2 ± 104.3	12 ± 6.5	45.7 ± 27.5	31.8 ± 68.2	<.0001[Ω]	4.6 ± 5.9	17 ± 12.9	58.9 ± 27.6	35.5 ± 31.7	<.0001[Ω]	NS[¥]
AHI during supine sleep	13.5 ± 18.2	33.6 ± 16.3	59.3 ± 26.0	37.3 ± 30.2	<.0001[Ω]	8.4 ± 12.0	39.4 ± 23.2	62.1 ± 22.5	44.5 ± 29.3	<.0001[Ψ]	NS[µ]
AHI during right-side sleep	2.8 ± 4.2	17.2 ± 10.3	37.7 ± 28.1	20.8 ± 25.1	<.0001[Ω]	1.4 ± 3.2	10.5 ± 9.5	55.3 ± 29.1	31.3 ± 32.4	<.0001[Ω]	NS[¥]
Total left-side sleep time	93.5 ± 71.1	114.8 ± 66.9	88.3 ± 68.9	94.8 ± 69.2	NS[Ψ]	78.2 ± 57.4	131.9 ± 81.9	140.0 ± 55.8	124.5 ± 66.8	NS[Ψ]	.05[µ]
Deep sleep time during left-side sleep	25.9 ± 36.4	27.9 ± 29.9	27.8 ± 34.1	27.1 ± 34.0	NS[Ω]	16.4 ± 17.5	45 ± 33.3	33.0 ± 39.3	32.9 ± 34.5	NS[Ω]	NS[¥]
Total supine sleep time	129.9 ± 97	103.7 ± 67.2	136.2 ± 111.0	128.4 ± 99.2	NS[Ω]	67 ± 45.9	69.4 ± 69	108.3 ± 75.7	88.4 ± 69.7	NS[Ψ]	.044[µ]
Deep sleep time during supine sleep	36.9 ± 47.4	18 ± 20.4	37.6 ± 50.3	34.1 ± 45.7	NS[Ω]	14.4 ± 18.8	12.6 ± 17.1	24.9 ± 49.0	19.1 ± 36.5	NS[Ω]	NS[¥]

[µ]Independent samples *t*-test; [¥]Mann–Whitney *U*-test; [Ψ]Kruskal–Wallis test, [Ω]ANOVA.
DM, type 2 diabetes mellitus; OSAS, obstructive sleep apnea syndrome; BMI, body mass index; NS, Nonsignificant.

Table 2. Multiple Comparisons Intra-Groups Analyses

	DM								
	Present				None				
Variables	*P*[Ω]	Group 1 vs. Group 2, *P**[,β]	Group 1 vs. Group 3	Group 2 vs. Group 3	Variables	*P*[Ω]	Group 1 vs. Group 2[β]	Group 1 vs. Group 3[β]	Group 2 vs. Group 3[β]
Prealbumin	.043[Ω]	NS[β]	NS[β]	.018[β]	A/H ratio-index (AHI)	<.0001[Ω]	<.0001[β]	<.0001[β]	<.0001[β]
A/H ratio-index (AHI)	<.0001[Ω]	.001[β]	<.0001[β]	<.0001[β]	Efficiency/Sleep	.009[Ω]	.035[β]	.004[β]	NS[β]
Total sleep time	.036[Ω]	NS[β]	.019[β]	NS[β]	Total count of apnea	<.0001[Ω]	.019[β]	<.0001[β]	<.0001[β]
Total count of apnea	.001[Ω]	.033[β]	.001[β]	.018[β]	Total count of hypopnea	<.0001[Ω]	<.0001[β]	<.0001[β]	.001[β]
Total count of hypopnea	<.0001[Ω]	.003[β]	<.0001[β]	<.0001[β]	Total count of apnea + hypopnea	<.0001[Ω]	<.0001[β]	<.0001[β]	<.0001[β]
Total count of apnea + hypopnea	<.0001[Ω]	.003[β]	<.0001[β]	<.0001[β]	Total count of central apnea	<.0001[Ω]	.051[β]	<.0001[β]	NS[β]
Total count of central apnea	.037[Ω]	NS[β]	.026[β]	NS[β]	Total count of obstructive apnea	<.0001[Ω]	.024[β]	<.0001[β]	<.0001[β]
Total count of obstructive apnea	<.0001[Ω]	.006[β]	.001[β]	.005[β]	Total count of mixed apnea	<.0001[Ω]	NS[β]	<.0001[β]	.001[β]
Total count of mixed apnea	.008[Ω]	NS[β]	.006[β]	.03[β]	Non-REM ratio	.026[Ω]	.045[β]	NS[β]	.004[β]
Non-REM ratio	.044[Ω]	.031[β]	.035[β]	NS[β]	Ratio of non-REM stage 1	.006[Ω]	NS[β]	.002[β]	NS[β]
REM ratio	.044[Ω]	.031[β]	.035[β]	NS[β]	REM ratio	.025[Ω]	.044[β]	NS[β]	.004[β]
Non-REM-AHİ	<.0001[Ω]	.001[β]	<.0001[β]	<.0001[β]	Non-REM-AHİ	<.0001[Ω]	<.0001[β]	<.0001[β]	<.0001[β]
REM-AHI	.029[Ω]	NS[β]	.032[β]	.033[β]	REM-AHİ	<.0001[Ω]	<.0001[β]	.001[β]	NS
Index of Apnea	.001[Ω]	.029[β]	.002[β]	.025[β]	Index of apnea	<.0001[Ω]	.044[β]	<.0001[β]	<.0001[β]
AHI of left-side sleep	<.0001[Ω]	NS[β]	.002[β]	.002[β]	Index of hypopnea	<.0001[Ω]	<.0001[β]	<.0001[β]	<.0001[β]
AHI of right-side sleep	<.0001[Ω]	.039[β]	<.0001[β]	<.0001[β]	AHI of left-side sleep	<.0001[Ω]	.004[β]	<.0001[β]	<.0001[β]
Index of hypopnea	<.0001[γ]	.034[§]	<.0001[§]	.001[§]	AHI of right-side sleep	<.0001[Ω]	<.0001[β]	<.0001[β]	.008[β]
AHI of supine sleep	<.0001[γ]	.026[§]	<.0001[§]	.045[§]	AHI of supine sleep	<.0001[Ω]	<.0001[β]	<.0001[β]	.001[β]
HGI	NS[Ω]				HGI	NS[Ω]			
HBA1c	NS[Ω]				HBA1c	NS[γ]			
Pred-HBA1c	NS[Ω]				Pred-HBA1c	NS[γ]			

[γ]ANOVA; [Ω]Kruskal–Wallis test; [§]Tukey's HSD; [β]Mann–Whitney *U*-test.
NS, Nonsignificant.

Table 3. Correlation of HGI Between the Variables

		DM: Present										DM: None									
Variables	Pred-HBA1C[α]	HAB1C[α]	Glucose[α]	Hgb[α]	Rbc[α]	Ratio of Non-REM, Phase 3[β]	Deep Sleeping Time During Supine Sleeping[β]	BMI[β]	HAB1C[β]	Total Count of Apnea[β]	Total Count of Central Apnea[β]	Total Count of Obstructive Apnea[β]	Total Count of Mixed Apnea[β]	Ratio of Non-REM, Phase 1[β]	Index of Apnea[β]	Total Supine Sleeping Time[β]	Deep Sleeping Time During Supine Sleeping[β]
HGI	$P=.040$	$P=.016$	$P=.040$	$P=.011$	$P=.012$	$P=.043$	$P=.011$	$P=.027$	$P<.0001$	$P=.001$	$P=.024$	$P=.002$	$P=.007$	$P=.001$	$P=.007$	$P=.001$	$P=.017$
	r = −0.377	r = 0.438	r = −0.377	r = −0.459	r = −0.454	r = 0.372	r = 0.455	r = 0.239	r = 0.719	r = 0.349	r = 0.245	r = 0.331	r = 0.289	r = −0.351	r = 0.288	r = 0.357	r = 0.258

[α]Spearman's rho; [β]Pearson.

Despite this information, the relationship between HGI and OSAS parameters has not been studied sufficiently in the literature, and our study aimed to address this issue and to investigate this relationship. Based on the previous studies, HGI is expected to be significantly associated with parameters related to the severity of the disease in patients with diabetic OSAS. In our study, the non-diabetic group with fewer literature data was accepted as the main group.[22,23] As expected and supported by the previous data, there was a significant difference in HGI level between the diabetic OSAS group and the non-diabetic group (T2DM and non-DM HGI: 1.380 ± 1.7 vs. 0.347 ± 0.25, $P < .0001$). The HbA1c, predicted HbA1c, and fasting blood glucose were also higher in the DM group ($P < .05$ for all). Thus, our study is the first one to examine HGI in OSAS in the literature. Interestingly, intragroup evaluation according to the severity of OSAS showed no significant correlation between increased severity of OSAS and HGI, both in the T2DM and the non-DM groups (all showing $P > .05$). Our results were supported by previous studies, in which no significant variation was found in HbA1c levels according to OSAS severity.[16,17] Considering the relationship between DM and REM and non-REM OSAS, different results have been interpreted in previous studies. In diabetic patients, sleep is associated with increased deterioration in the regulation of blood glucose along with increased HbA1c levels during the REM period.[22,23] Kurosawa et al.[7] found that increased non-REM-AHI was associated with HbA1c in non-diabetics. In our study, non-REM-AHI, and REM-AHI values did not show significant differences between the diabetic and non-diabetic groups ($P < .05$ for all, Table 1). Among the groups, only total supine time increased in the non-diabetic group (non-DM vs. T2DM, $P = .044$, Table 1). On examining the groups with and without DM separately among themselves, HGI and HbA1C parameters in the diabetic OSAS group did not show a significant increase with the severity of OSAS, while many other variables showed a significant difference in the severe diabetic OSAS group compared to the mild and moderate diabetic OSAS groups (Table 2). The same situation was observed in the non-diabetic patient group as well (Table 2). Significant positive correlations were also found between HGI and many OSAS parameters in the diabetic and non-diabetic groups (Table 3). In previous studies, which had different results, more REM-AHI in the DM group and non-REM-AHI in the non-DM group were shown to have a significant relationship with HbA1c.[7,22,23] The nocturnal respiratory events are more common in REM sleep, possibly due to greater relaxation of pharynx muscles in the REM sleep period along with reduced respiratory response to hypercapnic and/or hypoxic response. In the REM period, increased amounts of sympathetic activity and cardiovascular irregularities were detected compared to the non-REM period. In the long term, respiratory disorders in the REM period showed more negative effects than the non-REM period in terms of insulin resistance and glycemic control. Thus, the relationship between the severity of REM-AHI, metabolic syndrome, increased HbA1C, and insulin resistance in T2DM patients has been clearly demonstrated.[7,24] In another study, a significant relationship was found between REM-AHI and diabetic retinopathy, but no significant relationship was found with non-REM-AHI (OR for REM-AHI: 3.887; 95% CI: 0.737-20.495, $P = .024$). Additionally, a significant correlation was found between REM-AHI and diabetic nephropathy ($P = .03$). REM-AHI ≥30 has been associated with increased carotid intima thickness.[25-27] Similarly, in the study conducted by Koo et al.,[28] REM-AHI ≥15/h was considered as an

independent predictor of metabolic syndrome (OR: 7.08; 95% CI, 1.60-31.41; $P = .010$). Interestingly, in another study, a significant relationship was found between non-REM-AHI and HbA1c levels in the non-diabetic patients.[7]

REM OSAS may play an important role in the development of diabetes; however, non-REM OSAS shows no effect on glucose concentration. An increase was observed in the mean HbA1c levels, from 6.3% to 7.3%, in subjects with REM-AHI>47 events/hour compared to the REM-AHI<12, 3 events/h. Non-REM-AHI was not associated with HbA1c.[29] Besides these studies, REM-AHI was also found to be associated with an increase in levels of HbA1c in T2DM but was not associated with non-REM-AHI.[22,23] Interestingly in non-diabetic patients, the non-REM-AHI was found to be significantly associated with HbA1c levels rather than REM-AHI,[7] which is also supported by our study results.

Limitations

The results of this study are from cross-sectional data analysis. This design could potentially lead to missing data or biases. Moreover, in the absence of the control group (patients without OSAS), it is difficult to ascertain the associations between sleep and blood glucose parameters. Thus, our results should be further confirmed in prospective/controlled series. Moreover, our study included a small population, and we did not consider the factors of medical treatment and tobacco smoking, which variably could affect insulin resistance and risk of diabetes. Finally, we did not examine the effect of CPAP treatment on glucose metabolism in OSAS patients, which produced conflicting results among studies.

CONCLUSION

Our study investigated the relationship between OSAS parameters and HGI in DM and non-DM groups diagnosed with OSAS and found a difference between the groups in terms of HGI. In the analysis of the groups according to the severity of OSAS, no significant relationship was found between HGI and OSAS severity.

Ethics Committee Approval: The approval for the study was obtained from the Ethics Board of Ahi Evran University, Faculty of Medicine, with the decision no: 2019-20-197, dated November 26, 2019.

Informed Consent: A written consent was obtained from all the patients who participated in the study.

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