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Glucose profiles in obstructive sleep apnea and type 2 diabetes mellitus

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ABSTRACT

Objectives: Continuous glucose monitoring (CGM) provides temporal data on glycemic variability, a predictor of outcomes related to type 2 diabetes mellitus. The current study sought to determine whether CGM-derived metrics in patients with type 2 diabetes are different in moderate-to-severe versus mild obstructive sleep apnea (OSA).

Methods: In adults with type 2 diabetes, home testing was used of assess the presence of OSA. CGM data were collected for at least 7 days in those with an oxygen desaturation index (ODI) $\geq$ 5 events/hr. The study sample was divided into mild (ODI: 5.0–14.9 events/hr) and moderate-to-severe OSA (ODI $\geq$15 events/hr). Actigraphy was used to distinguish the wake and sleep periods. CGM-derived metrics were compared between the two groups using multivariable regression models.

Results: Compared to mild OSA, patients with moderate-to-severe OSA had higher mean glucose levels during sleep (adjusted difference 8.4 mg/dL; p-value: 0.03) and wakefulness (adjusted difference 7.1 mg/dL; p-value: 0.06). Moderate-to-severe OSA patients also had lower odds for having their glucose values within the acceptable range during wakefulness than those with mild OSA (adjusted odds ratio of 0.63; p-value: 0.02). The mean amplitude of glycemic excursion and standard deviation of the rate of change in glucose values (SD-ROC) were higher in moderate-to-severe than mild OSA, but only during wakefulness. Sex modified the association between OSA severity and SD-ROC, but not the other CGM-derived metrics.

Conclusions: In patients with type 2 diabetes, moderate-to-severe OSA is associated with greater abnormalities in CGM-derived metrics than mild OSA with notable differences between sleep and wakefulness.

1. Introduction

Obstructive sleep apnea (OSA) is relatively common in patients with type 2 diabetes mellitus with prevalence estimates in the range of 54–86% [1,2]. Clinical and epidemiological studies have demonstrated that OSA is independently associated with insulin resistance, glucose intolerance, and incident type 2 diabetes [3–6]. Randomized clinical trials, however, have not consistently shown that therapy with positive airway pressure (PAP) for OSA in patients with type 2 diabetes improves glycemic control as assessed by hemoglobin A1c (HbA1c) [7–11]. While HbA1c is a relatively simple and clinically useful metric of glycemic control predictive of incident vascular complications [12,13], it alone may not fully characterize the impact of OSA on glycemic status given that it integrates glucose levels over several preceding months. Continuous glucose monitoring (CGM) on the other hand provides high-resolution temporal data on glucose levels over several days or even weeks. Thus, CGM data are complimentary to HbA1c and can be used to assess glycemic variability, which is being increasingly recognized as a predictor of vascular complications even in those with well-controlled type 2 diabetes [14–20].

An array of glucose metrics can be derived from CGM based on prespecified time frames (e.g. wake or sleep). While some of the CGM-derived metrics, such as mean glucose values or time duration where glucose is within a given range over specific periods,

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Abbreviation list

BMI	Body mass index
CGM	Continuous glucose monitoring
CV	Coefficient of variation
HbA1c	Hemoglobin A1c
MAGE	Mean amplitude of glycemic excursion
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
SD	Standard deviation
SD-ROC:	Standard deviation of the rate of change
TIR	Time in range

summarize the natural history of glucose levels, others depict the trends in glucose levels within a shorter period (e.g. mean amplitude of glycemic excursion, standard deviation of the rate of change). Accordingly, CGM-derived metrics can describe the time-varying nature of glucose levels analogous to the measures which are derived from 24-h ambulatory monitoring of blood pressure. With availability of data over several days or weeks, the role of OSA in circadian-related changes in glucose levels can be probed similar to what has been done with 24-h blood pressure [21–23]. A challenge in the analysis of temporal data on glucose is to determine which metrics are independently influenced by OSA severity. Furthermore, given that glycemic profiles are determined by other factors such as meals during wakefulness and perhaps by OSA-associated nocturnal hypoxemia, construing 24-h data on glucose during wakefulness and sleep has pathophysiologic and clinical value. Thus, the overarching objective of this study was to examine which CGM-derived metrics are independently associated with OSA in patients with type 2 diabetes and determine whether observed associations differ during wake and sleep periods.

2. Materials and methods

2.1. Sample selection

Adults between the ages of 21–75 years with type 2 diabetes were recruited for screening, which included a point-of-care hemoglobin A1c (HbA1c) measurement with the DC Vantage Analyzer® (Siemens Malvern PA). A HbA1c value $\geq$ 6.5% was required for further screening. A home sleep apnea test with the Apnealink® (Resmed, San Diego, CA) was conducted next, and only those patients with OSA, defined as an oxygen desaturation index (ODI) $\geq$ 5 events/hr, were enrolled. Exclusionary criteria included pregnancy, ongoing therapy for OSA, insulin use, change in glycemic medications in the previous six weeks, current oral steroid use, other sleep disorders, habitual sleep duration of <6 h/night, or any unstable medical condition requiring hospitalization in the prior three months. The research protocol was approved by the Institutional Review Board on human research (Number: NA_00093188). Details regarding the study design and sample selection have been previously reported [24].

2.2. Home sleep apnea test and actigraphy

Respiratory polygraphy was conducted using a type 3 monitor (Apnealink®). This device was provided to evaluate for OSA with a minimum recording threshold of 4 h duration for an acceptable recording. Pulse oximetry was used to assess oxyhemoglobin saturation, respiratory effort was measured with a pneumatic sensor attached to an effort belt, and nasal airflow as recorded with a nasal cannula connected to a pressure transducer. An oxygen desaturation of 4% or more was used to determine the ODI. Each recording was manually scored and reviewed by a board certified physician in Sleep Medicine. Sleep-wake activity monitoring was performed with the Actiwatch (Philips Respironics, Murraysville, PA). Participants were instructed to wear the Actiwatch on the non-dominant wrist for at least seven 24-h periods (minimum of 5 nights, including at least one weekend/non-workday period). Actigraphy recordings were scored using an automated algorithm and subsequently reviewed by one of the investigators to distinguish periods of sleep from wake.

2.3. CGM-derived measures

Participants wore the DexCom G4 Platinum CGM device and interstitial glucose was measured every 5 min for up to 14 days. Calibrations for the G4 sensor were performed using capillary blood glucose values measured at least twice per day with a FreeStyle InsuLinx glucometer (Abbott Diabetes Care, Inc, Alameda, CA). The overall mean glucose value from all of the available CGM data was derived along with the time in range (TIR [70, 180] mg/dL). The standard deviation (SD) of glucose and coefficient of variation (CV) were also determined and, in conjunction with the mean and TIR, were used as overall or summary measures of glucose variability. In addition, mean amplitude of glycemic excursion (MAGE) [25] and the SD of the rate of change (SD-ROC) [26] were used to characterize variations in glucose values. To derive SD-ROC, the rate of change of glucose at each time point was first calculated by computing the difference in glucose (Δg) over a 15 min interval ($\Delta g/\Delta t$).

2.4. Statistical analysis

Multivariable linear models were used to examine the association between OSA severity (i.e., ODI) and CGM-derived metrics. Variables with skewed distributions (i.e., TIR) were transformed using log odds for normality. OSA severity was classified as mild (ODI: 5.0–14.9 events/h) or moderate-to-severe (ODI $\geq$15 events/hr). To assess the independent association between ODI category and each of the CGM-derived metrics, age, sex, race, BMI, use of hypoglycemic medications, and HbA1c were included in all of the models. Models were initially developed using the entire 24-hr period and subsequently stratified by wake versus sleep periods. The distinction of wake versus sleep was based on data derived from concurrent activity monitoring. Interaction terms between sex and ODI category were included along with the main effects in the multivariable models to assess for heterogeneity of associations between ODI and the panel of CGM-derived metrics. Forest plots were used to visualize effect sizes. All CGM metrics were calculated using the R package iglu v.2.0.0 [27] and conducted in R version 4.0.2.

3. Results

The study sample consisted of 207 patients with type 2 diabetes and OSA. The average age of the sample was 61.0 years (interquartile range [IQR]: 53.5–67.0 years). Just over half the sample was male (54%). Most participants were on at least one oral hypoglycemic agent and had fairly well controlled diabetes given the mean HbA1c of 7.2%. The median number of days of CGM use was 11 days. Approximately, 50% of the sample had mild OSA with the remaining having moderate-to-severe OSA. Table 1 shows baseline characteristics of the study sample stratified by OSA severity. Fig. 1 graphically depicts the calculation of MAGE and SD-ROC. MAGE describes the average of the consecutive peak to trough differences

Table 1
Characteristics of the study sample (N = 207).

Variable	Full Sample (N = 207)		Mild OSA (N = 104)		Moderate OSA (N = 103)		p-value
Age, years	61.0	(53.5–67.0)	62.0	(54.0–67.0)	60.0	(53.0–66.0)	0.41
BMI, kg/m^2	32.9	(30.1–37.2)	31.8	(28.8–36.4)	34.5	(31.0–37.3)	0.01
Male sex	112	(54.1%)	54	(52.0%)	58	(56.3%)	0.53
Race							
White	112	(54.1%)	59	(56.7%)	53	(51.5%)	0.71
Black	72	(34.8%)	34	(32.7%)	38	(36.9%)	0.71
Other	23	(11.1%)	11	(10.6%)	12	(11.6%)	0.71
ODI, events/hr	14.9	(10.7–23.6)	10.7	(8.6–12.5)	23.7	(18.4–36.6)	<0.0001
HbA1c, %	7.2	(6.9–7.8)	7.3	(6.9–7.8)	7.2	(6.8–7.8)	0.44
Biguanide	175	(84.5%)	91	(87.5%)	84	(81.5%)	0.24
Sulfonylurea	71	(34.3%)	34	(32.7%)	37	(36.0%)	0.63

Values are the medians (interquartile range: 25–75th percentile) or N (%); p-value reported for comparing mild to moderate-to-severe OSA.

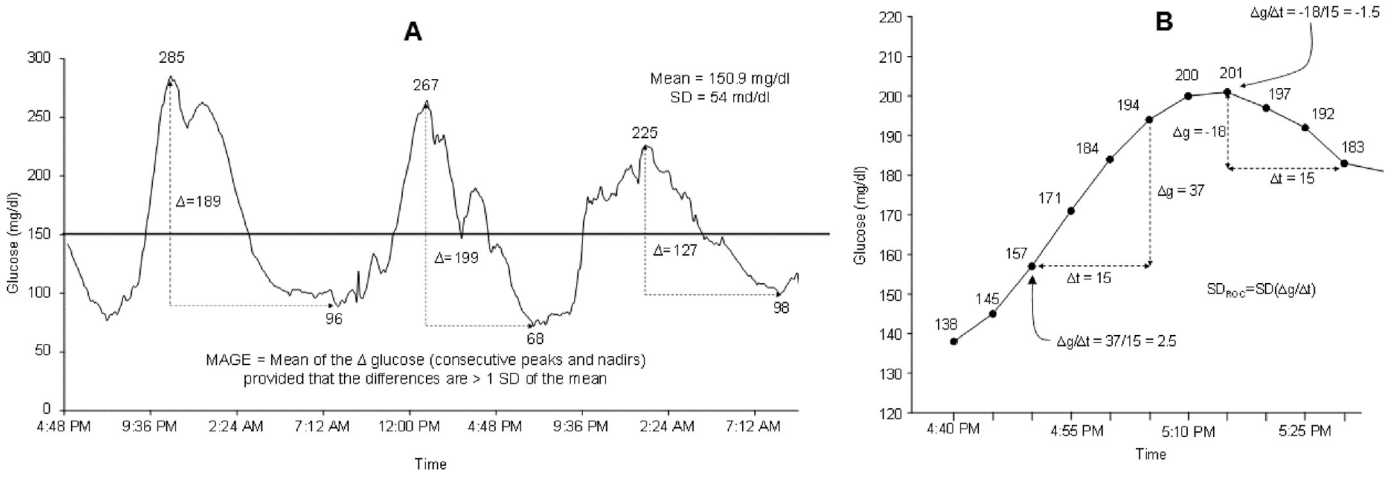


Fig. 1. Graphical illustration for calculation of mean amplitude of glycemic excursion (MAGE) [panel A] and standard deviation of the rate of change (SD-ROC) [panel B].

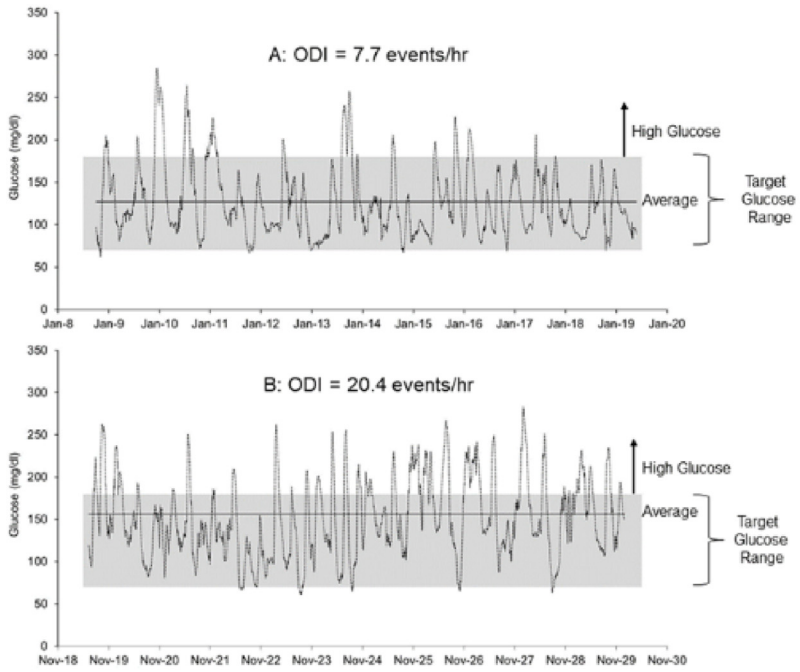
in glucoses whereas SD-ROC portrays the spread of rate of change values, with higher values of SD-ROC indicating high frequency of rapid glucose changes, and lower values of SD-ROC indicating slower changes (i.e., more stable glucose dynamics). Fig. 2 shows representative CGM profiles from two participants (mild versus moderate OSA) and the associated derived measures including mean glucose, TIR, SD, CV, MAGE and SD-ROC.

Regression coefficients derived from multivariable models corresponding to each CGM measure are displayed in Figs. 3–5. Fig. 3 is a forest plot for models corresponding to overall measures of glucose control (MEAN and TIR). Patients with moderate-to-severe OSA had a significantly higher mean glucose values (adjusted difference 7.4 mg/dL; p-value: 0.041) and TIR (adjusted odd ratio 0.67; p-value: 0.039) indicating that those with an ODI ≥15 events/hr had higher mean glucose values and a lower percentage of time the glucose values were within the acceptable range. The association between OSA severity and mean glucose values was more pronounced during the sleep period (adjusted difference 8.4 mg/dL; p-value: 0.03) than during wakefulness (adjusted difference 7.1 mg/dL; p-value: 0.06). In contrast, the association between OSA severity and TIR was more pronounced during wakefulness (adjusted odds ratio 0.63; p-value: 0.02) compared to the sleep period (adjusted odds ratio 0.71; p-value: 0.24). Among patients with moderate-to-severe OSA, the TIR was lower by 9% compared to those with mild OSA. An interaction between ODI category and sex was not observed for either mean glucose values or TIR. Other variables associated with a high mean glucose value and a lower TIR were HbA1c and being on a sulfonylurea or biguanide. Otherwise, no other consistent associations were noted with age, BMI, race, or sex.

Glycemic variability, as determined by SD and CV, was also examined as a function OSA severity. Fig. 4 displays forest plots for these models illustrating that OSA severity was not significantly associated with either SD (p-value: 0.11) or CV (p-value: 0.66). Furthermore, the interaction between ODI and sex was not significant for either glucose variability metrics. Models corresponding to dynamic measures, which consider temporal dependencies (MAGE and SD-ROC), are shown in Fig. 5. Compared to mild disease, moderate-to-severe OSA was associated with both MAGE (adjusted difference 6.8 mg/dL; p-value = 0.033) and SD-ROC (adjusted difference 0.03 mg/dL/min; p-value: 0.05). Moderate-to-severe OSA was associated with higher values of MAGE and SD-ROC, signifying greater variations in glucose levels. The association was pronounced during wake periods (adjusted MAGE difference: 8.2 mg/dL [p-value: 0.03] and adjusted SD-ROC difference: 0.04 mg/dL/min [p-value: 0.05]) but not observed during the sleep period. The interaction between ODI and sex was not significant for MAGE (p-value: 0.50). In contrast, an interaction between sex and OSA was significant for SD-ROC with women with moderate-to-severe OSA having a SD-ROC value higher by 0.07 mg/dL/min than men with moderate-to-severe OSA (p-value: 0.04 of interaction).

4. Discussion

The results of the current study demonstrate several findings regarding the potential influence of OSA severity on various CGM-derived metrics in patients with type 2 diabetes mellitus. First, patients with moderate-to-severe OSA had higher mean glucose values and less time with glucose values in the acceptable range



CGMS Metric	A	B
Mean glucose (mg/dl)	127.0	155.0
Time in range, %	88.0	68.0
Standard deviation, mg/dl	42.2	48.6
Coefficient of variation, %	33.3	31.1
MAGE, mg/dl	101.0	116.0
Standard deviation$_{ROC}$	0.7	0.9

Fig. 2. Characteristic glucose profiles of a patient with mild OSA (ODI: 7.7 events/hr) and moderate OSA (ODI: 20.4 events/hr) with corresponding calculations of various CGM metrics.

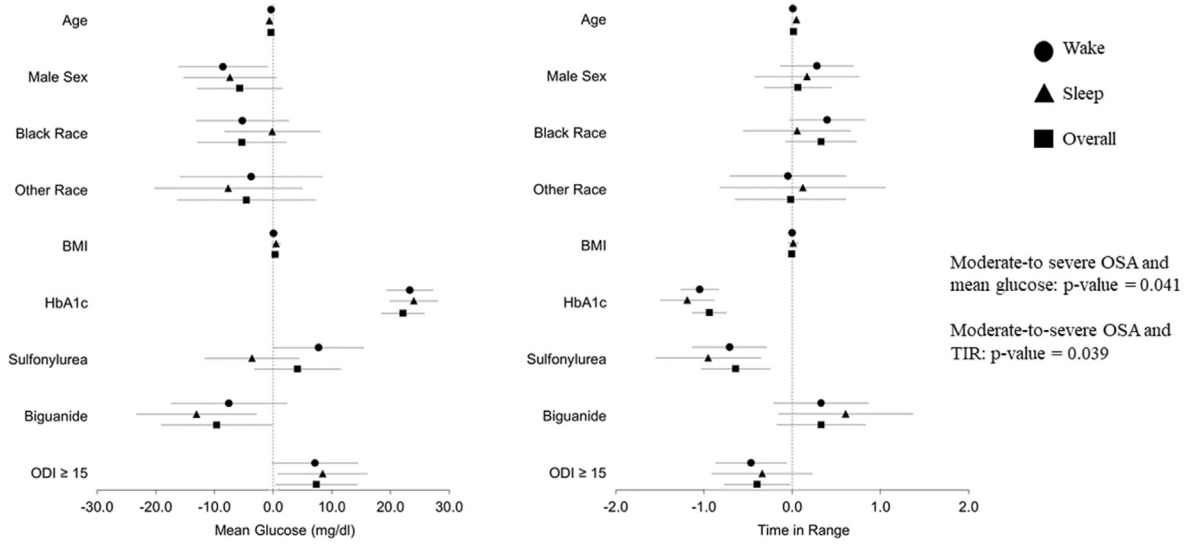


Fig. 3. Forest plots of mean glucose and TIR (log odds).

(TIR: 70–180 mg/dl) compared to patients with mild OSA. Second, dynamic CGM measures, such as MAGE and SD-ROC, were also found to be higher in moderate-to-severe than mild OSA. The observed associations between OSA and CGM metrics varied as a function of sleep-wake state. Finally, sex-based differences were also seen in the association but only for OSA and SD-ROC. Both of the latter findings are unique observations that have not been previously reported.

The findings noted herein add to the growing body of evidence on the impact of OSA on glucose metabolism in type 2 diabetes by examining both overall summary measures as well as dynamic CGM-derived metrics (i.e., SD-ROC), and by stratifying the associations by actigraphy-based assessments of wake and sleep. Currently, the evidence examining the associations between OSA and CGM-derived metrics in type 2 diabetes is limited and inconsistent. A few studies have shown that OSA metrics such as the apnea-hypopnea index and nocturnal oxygen desaturation are associated with CGM-derived 24-h MAGE [28], nocturnal MAGE [28], nocturnal average and peak glucose levels [29], and postprandial fluctuations [30]. Yet, other studies have not demonstrated any associations between OSA and CGM-derived metrics in patients with type 2 diabetes [31,32]. In the present study, moderate-to-severe OSA was associated with a higher overall (24-h) mean glucose, which was driven by a higher mean glucose value specifically during the sleep period. Amongst the other CGM-derived metrics assessed in the current study, TIR, MAGE, and SD-ROC

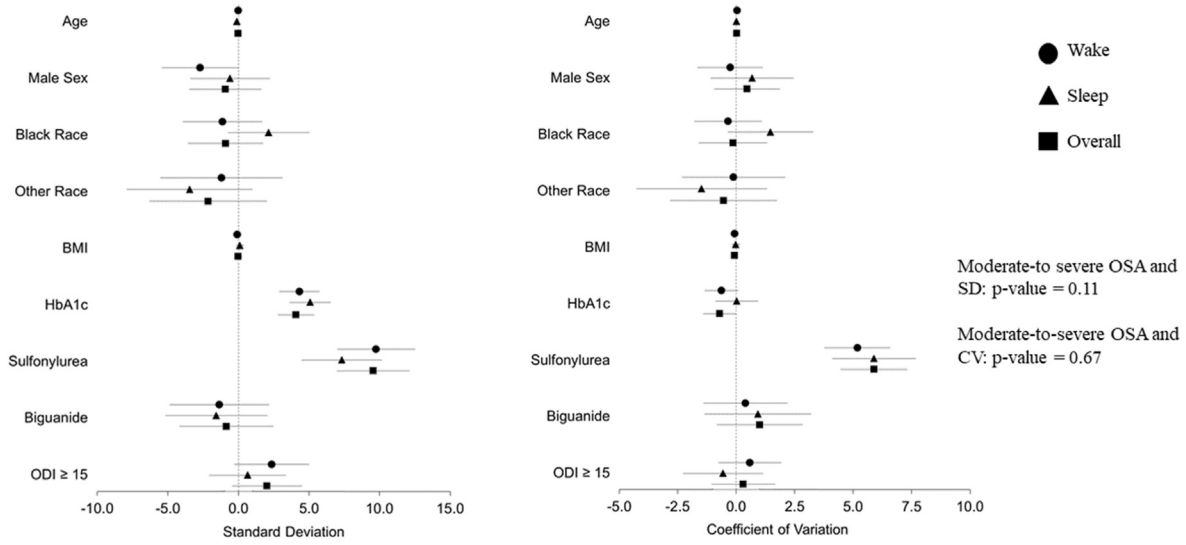


Fig. 4. Forest plots of SD and CV.

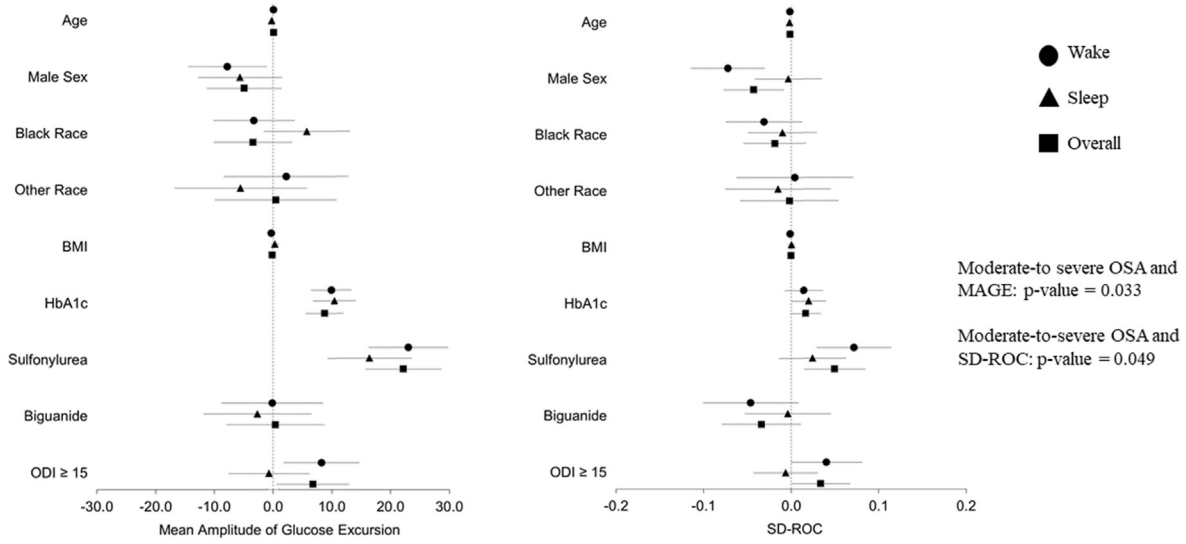


Fig. 5. Forest plots of MAGE and SD-ROC.

were also higher in moderate-to-severe than in mild OSA, but in contrast to the mean glucose, these were driven by glucose values during wakefulness. A decrease of 10% in TIR has been found to be associated with an increased risk of developing microvascular complications. In the Diabetes Control and Complications Trial (DCCT), the adjusted hazards ratios of developing retinopathy and microalbuminuria in those with type 2 diabetes were 1.64 (95% CI: 1.51, 1.78) and 1.40 (95% CI: 1.25, 1.56), respectively, when the TIR was reduced by 10% [33]. Thus, a reduced TIR of 9% in persons with type 2 diabetes and moderate-to-severe OSA noted in the current study has potential clinical significance. Because TIR, MAGE, and SD-ROC are influenced by large glucose oscillations, these measures more aptly depict glycemic variability. Several factors during wakefulness (e.g. food intake and hypoglycemic medication use) can contribute to large fluctuations in glucose levels. OSA may further exacerbate these excursions with prolonged and elevated postprandial glucose levels through the effects of increased sympathetic nervous system activity, which can impair homeostatic processes that regulate glucose disposal. In contrast, during sleep where there are no extrinsic challenges (e.g., food intake), OSA-related intermittent hypoxemia and recurrent arousals may be sufficient to cause large variations in glucose levels. While previous studies have examined CGM data over 24-hr and fixed-time nocturnal periods presumed to reflect sleep, there has been no differentiation between wake and sleep using objective data (i.e., actigraphy or polysomnography).

Of all of the CGM-derived metrics described in this study, SD-ROC is the most dynamic measure that informs about the homeostatic response to glycemic challenges by characterizing the behavior of glucose levels over short periods. It offers a unique assessment of the variability in glucose levels because it focuses on the change in glucose over an abbreviated time interval (e.g., 15 min) yet summarizes that behavior across longer periods (e.g., days or weeks). Similar to identifying the loss of sleep-related dipping in blood pressure as an early step in the pathogenesis of hypertension in OSA, a time-varying metric of glucose metabolism such as SD-ROC could also depict the earliest, most granular, and yet clinically relevant data on glycemic perturbations in OSA. High

variations in glucose levels can trigger oxidative stress and subclinical inflammation [14,34–39], thereby potentially contributing to adverse health outcomes when OSA and type 2 diabetes are coexistent. Moreover, in patients with both disorders, SD-ROC may help identify those who are most susceptible to glycemic perturbations due to OSA and possibly most at risk for deterioration in glycemic control (i.e. worsening HbA1c) and/or the development of cardiovascular complications.

There are several strengths and limitations of the present study that warrant discussion. Strengths include enrollment of a diverse, community-based patient sample that adds to the generalizability of the findings and the use of a wide array of CGM metrics over multiple days thereby providing a comprehensive assessment of glycemic status. Use of actigraphy is another strength that helped to define associations between OSA and glycemic control as function of the wake and sleep periods. Furthermore, accounting for the use of hypoglycemic medications in the analyses uncovered independent associations between OSA and CGM outcomes. Finally, the inclusion of a significant number of women allowed for analyses on sex-based differences in glycemic outcomes. Limitations include the use of home-based sleep testing that does not provide information on EEG, therefore associations between EEG-based arousals or sleep stages and glycemic metrics could not be delineated. Other limitations to consider are the absence of data on nutritional intake and physical activity, both of which may contribute to variability in glycemic outcomes. Furthermore, while hypoglycemic medications were included in the analyses, differences in individual response to medication are possible but could not be determined. Finally, subjects had relatively well controlled type 2 diabetes as evidenced by a mean HbA1c of 7.2%. Thus, the findings cannot be extrapolated to persons with poorly controlled type 2 diabetes.

In summary, the current demonstrates that different CGM-derived metrics provide distinct information about glycemic variations in patients with OSA and type 2 diabetes. Leveraging these differences can help to further elucidate the role of OSA in altering metabolic function particularly in OSA treatment-related randomized clinical trials. Furthermore, the information presented herein suggests that the impact of OSA on glucose metabolism need to be stratified by wake and sleep periods given that specific exposures (i.e. meals, medications, OSA-related intermittent hypoxemia) also vary across the 24-h period.

5. Conclusion

To uncover the association between OSA and altered glucose metabolism, careful deliberation of the specific CGM-derived metrics utilized and the time frame of analysis should be considered in future studies on the role of OSA or its treatment on glucose metabolism.

Conflict of interests

None.

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CRediT authorship contribution statement

R. Nisha Aurora: Formal analysis, Writing – review & editing, contributed significantly to the study design, Data curation. **Irina Gaynanova:** Formal analysis, Writing – review & editing, and contributed significantly to the study design, Data curation. **Pratik Patel:** Formal analysis, Writing – review & editing, contributed significantly to the study design. **Naresh M. Punjabi:** Formal analysis, Writing – review & editing, and contributed significantly to the study design, Data curation.

Declaration of competing interest

None.

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