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Relation between the Severity of Obstructive Sleep Apnea and the Severity of Type 2 Diabetes Mellitus and Hypertension

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Abstract

Background: Obstructive sleep apnea syndrome (OSAS) may promote hyperglycemia, insulin resistance, and hypertension (HTN). **Purpose:** To evaluate if there is a relationship between the severity of OSA and the severity of type 2 diabetes mellitus (T2DM) and HTN in our patients, aiming to understand and optimize the control for comorbidities. **Materials and Methods:** Patients referred for polysomnography (PSG) were retrospectively recruited during the period from October 2017 to August 2020. A STOP-BANG questionnaire formed eight questions was used to assess the risk of OSAS. We divided the patients into two groups; group 1, who have snoring without T2DM, and group 2, who have snoring with T2DM. PSG was completed for all subjects and data were collected for each patient including apnoea hypopnea index (AHI), mean arterial oxygen saturation (SaO_2), and Nadir SaO_2 recorded during PSG. Anthropometric data, medical history, and medications for T2DM (for group 2) and HTN and HbA1c were collected (for group 2). AHI was used to evaluate the severity of OSA and its relation to T2DM and HTN. **Results:** The study included 300 patients who met the inclusion criteria with mean age of 49.9 ± 13.6 years. The majority of subjects (56.3%) were males and the mean body mass index (BMI) was 38.0 ± 8.4 kg/m^2. Forty-two percent had HTN and 32.7% had T2DM. OSA was diagnosed in 209 patients (69.7%). OSA was more detected among those with increased age, increased BMI, and those with HTN and T2DM. The severity of both HTN and T2DM

was significantly higher among patients with OSA. **Conclusions:** There is a relation between OSA and T2DM and HTN. The risk of OSA is higher among patients with uncontrolled T2DM and HTN. OSA should be suspected in subjects with obesity, especially with uncontrolled HTN and T2DM.

Keywords

Obstructive Sleep Apnea, Apnea-Hypopnea Index, Type 2 Diabetes Mellitus, Hypertension

1. Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, characterized by repetitive episodes of upper airway closure or partial collapse during sleep, resulting in intermittent hypoxia and fragmented sleep. OSA is a recognized risk factor for insulin resistance and type 2 diabetes mellitus (T2DM), independently of body mass index (BMI) [1]. In well-designed laboratory experiments, intermittent hypoxia and fragmented sleep resulted in increased insulin resistance without an adequate compensatory insulin response, leading to glucose intolerance [2] [3]. Furthermore, a recent meta-analysis of over 60,000 participants from nine prospective cohort studies revealed that OSA was associated with a 35% increase in the risk of developing T2DM [1].

The estimated overall prevalence of OSA has substantially increased, and it is highly prevalent in patients with T2DM, between 58% - 86%, depending on the study population [4] [5], particularly in patients with severe obesity [6]. In patients with T2DM, OSA severity has been shown to be associated with worse glycemic control [7] [8].

Similarly, the prevalence of T2DM is high in patients with OSA (15% - 30%) [9]. Given such high prevalence, in 2008, the International Diabetes Federation (IDF) recommended routine screening for OSA in patients with T2DM. However, despite the IDF statement, a recent survey in the United Kingdom showed that two-thirds of diabetes healthcare professionals were unaware of these recommendations and only 19% had the local diabetes guidelines incorporated assessment for OSA in those at risk [10].

Over the years, there has been some overlap between patients with OSA and hypertension (HTN), with about 50% of HTN patients also having concomitant OSA. Therefore, it has been hypothesized that the two conditions may have a causal, bidirectional relationship [11]. This was further supported when OSA was stated as a secondary cause of HTN by the 2003 Joint National Committee (JNC VII) on prevention, detection, evaluation, and treatment of high blood pressure (BP) [12]. A few years later, the 2019 American Heart Association (AHA) reported the results of a meta-analysis of 27 cohort studies which showed that severe OSA (AHI ≥ 30) was associated with increased cardiovascular mortality with a hazard ratio of 2.73 (95% confidence interval [CI], 1.94 - 3.85) [13].

It is well known that OSA, especially moderate-to-severe degree, is strongly associated with HTN, and hypertensive patients with OSA are at a higher risk for adverse cardiovascular events [14]. HTN also plays a crucial role in diabetes-related complications; systolic BP has been shown to independently and additively exert effects on micro- and macrovascular complications in T2DM patients, in addition to glycemic control. It is likely that HTN at least partly mediates relationship between OSA and diabetes complications [15].

We aimed to evaluate if there is a relationship between the severity of OSA and the severity of T2DM and HTN in our patients, aiming to understand and optimize the control for comorbidities.

2. Participants & Methods

2.1. Design Study Area and Population

A retrospective database analysis of medical records of patients with OSA was performed at Almoosa Hospital, Alhasaa, Saudi Arabia, during the period from October 2017 to August 2020. Almoosa Hospital is the biggest tertiary care private hospital, including 300 beds in the Eastern region of Saudi Arabia. Patients were tracked across the inpatient (many cases were admitted due to acute exacerbation of obesity hypoventilation syndrome, and polysomnography (PSG) was done after stability either as inpatient or scheduled after discharge as outpatient) and outpatients (cases referred for PSG from pulmonology, ENT, internal medicine, nephrology, diabetic, neurology clinics), settings. Ethical approval was obtained from the Institutional Review Board at Almoosa Hospital, Saudi Arabia. Privacy and confidentiality were maintained throughout the study process.

The study population included all patients who visited our hospital during the study period with a chief complaint of snoring as witnessed by a sleep partner and who underwent overnight PSG. We divided the patients to two group; group 1: who have snoring without T2DM, and group: 2 who have snoring with T2DM.

The exclusion criteria: 1) patients younger than 14 years of age. 2) those diagnosed before as obstructive sleep apnea. 3) those had central sleep apnea. 4) who did tonsillectomy or uveoplataophyrngoplasty for treatment of sleep apnea.

2.2. Procedures

1) Assessment of baseline patients' characteristics including weight, height, BMI, neck circumference (cm), age, gender, and HTN medications (number of medications taken). For group 2: glycemic control, diabetes medications (number of medications taken) and most recent hemoglobin A1c (HbA1c) values (within three months) were extracted from patient medical records. HbA1c was used for measurement of blood glucose control over the preceding 90 days and was used as a clinical indicator of glucose control [16].

HTN was defined by systolic BP ≥ 140 mmHg and/or diastolic BP ≥ 90 mmHg, and/or the use of antihypertensive treatment (**Table 1**). Before diagnos-

ing a patient with HTN, physicians must base the diagnosis on the average value of more than two BP readings obtained on more than two different occasions [17].

Saudi HTN Guidelines and classification of HTN: the diagnostic threshold is BP ≥ 140/90 mmHg (Table 1).

Resistant HTN is high BP that does not respond well to aggressive medical treatment. HTN is considered resistant when all following are true:

- Someone is taking three different BP medications at their maximally tolerated doses.
- One of the BP medications is a diuretic (removes fluid and salt from the body).
- BP remains above your goal.
- If HTN requires four or more medications to be controlled, it is also called resistant HTN.
- Resistant HTN substantially increases the risk of heart attack, stroke, and kidney failure.

2) STOP-BANG questionnaire:

The Stop-bang questionnaire requires "yes" or "no" answers to eight questions about snoring, tiredness, observed apnea and BP, BMI > 35 kg/m^2, age > 50 years, and neck circumference > 17in. for males and 16in. for females. It worth noting that while the Stop-bang questionnaire grants the same score for any question, not all items have the same predictive value for OSA [18] [19].

Scoring criteria:

Low risk of OSA: Yes, with 0 to 2 questions; Intermediate risk of OSA: Yes, with 3 to 4 questions; High risk of OSA: Yes, with 5 to 8 questions.

3) Polysomnography (PSG):

An overnight PSG was performed on all patients in the sleep laboratory at Almoosa Hospital. Electroencephalography, electrooculography, electrocardiography, chin & tibial electromyography, oral-nasal airflow meter measured by thermocouples, and nasal pressure, oxyhemoglobin saturation measured by finger pulse oximeter, chest and abdominal movements measured by respiratory inductive plethysmography, body position, and snoring noise captured by a microphone, were recorded. Digital video recording was performed throughout the night. The PSG recordings were analyzed by a certified PSG technologist.

Table 1. Saudi hypertension guidelines and classification of hypertension.

Blood Pressure Category	Systolic (mmHg)	Diastolic (mmHg)
Optimal Blood Pressure	Less than 120	Less than 80
Normal	120 - 129	80 - 84
Prehypertension	130 - 139	85 - 89
Stage (1) Hypertension	140 - 159	90 - 99
Stage (2) Hypertension	160 - 179	100 - 109
Stage (3) Hypertension	Higher than 180	Higher than 110

Apnea was defined as cessation of airflow for more than 10 seconds, and hypopnea was defined as a ≥50% decrease in airflow that persisted for more than 10 seconds and was accompanied by oxygen desaturation of 3% or greater or by arousal. AHI was calculated as the total number of respiratory events (apnea plus hypopnea) per hour of sleep [20]. Height, weight, and NC were determined on the night of sleep study. Height, in centimeters, was measured with a stadiometer. Weight in kilograms was measured with a scale. BMI was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). NC, in centimeters, was measured at the level of the cricothyroid membrane with a tape measure.

The diagnosis of OSA was made based on AHI > 5 with witnessed snoring or apnea [21] [22], which was used to divide the patients into two groups according to the presence and absence of apnea. In addition, we categorized the severity of sleep apnea based on the AHI (events per hour) into three groups: mild (AHI > 5 to ≤ 15), moderate (AHI > 15 to ≤ 30), and severe (AHI > 30).

2.3. Statistical Analysis of Data

Statistical analysis was carried out using the SPSS computer package version 25.0 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp., USA). For descriptive statistics: the mean ± SD was used for quantitative variables while frequency and percentage were used for qualitative variables. Chi-square test or Fisher's Exact test were used to assess the differences in frequency of qualitative variables, while Mann-Whitney test or Kruskal-Wallis test were used to assess the differences in means of quantitative nonparametric variables. The statistical methods were verified, aFssuming a significant level of $p < 0.05$ and a highly significant level of $p < 0.001$.

3. Results

The study included 300 patients who met the inclusion criteria with mean age of 49.9 ± 13.6 ranging from 14 - 87 years. Majority of subjects (56.3%) were males and the mean BMI was 38.0 ± 8.4 kg/m^2. Forty-two percent had HTN and 32.7% had T2DM. OSA (AHI > 5) was diagnosed in 209 patients (69.7%). Significantly, OSA was more detected among those with increased age, increased BMI, and those with HTN and T2DM. Severity of HTN (as indicated by the number of medications received) was significantly higher among patients with OSA (**Table 2**).

The mean sleep efficiency was 74.3 ± 16.5. The means of AHI and STOP-BANG scores were significantly higher, and Nadir O_2 saturations were significantly lower among patients with OSA (**Table 3**).

In patients with T2DM, no significant age or gender difference was detected regarding the presence or absence of OSA. However, patients with T2DM and OSA had significantly higher BMI, AHI, HBA1c and STOP-Bang scores and significantly lower Nadir O_2 saturation than diabetics without OSA. Majority

Table 2. General and clinical characteristics of the studied samples.

Variables		All cases n = 300	Without OSA n = 91	With OSA n = 209	P-value
Age (years)	Mean ± SD Min - Max	49.9 ± 13.6 14 - 87	41.7 ± 14.0	53.4 ± 11.8	<0.001*
Gender	Male	169 (56.3)	50 (54.9)	119 (56.9)	0.800
	Female	131 (43.7)	41 (45.1)	90 (43.1)	
BMI (kg/m²)	Mean ± SD Min - Max	38.0 ± 8.4 20.6 - 62.1	33.9 ± 7.6	39.7 ± 8.2	<0.001*
HTN		126 (42.0)	24 (26.4)	102 (48.8)	0.022*
Severity of HTN[1] (n = 126)	Monotherapy		12 (50.0)	22 (21.6)	0.016*
	2-line therapy		7 (29.2)	39 (38.2)	
	≥3-line therapy		5 (20.8)	41 (40.2)	
T2DM		98 (32.7)	20 (22.0)	78 (37.3)	0.011*
IHD		30 (10.0)	10 (11.0)	20 (9.6)	0.706
Other diseases[2]		131 (43.7)	45 (51.0)	86 (41.5)	0.182

BMI: Body mass index, HTN: Hypertension, T2DM: Type 2 diabetes mellitus, IHD: Ischemic heart disease. [1]: Only among HTN cases (n = 126; 24 without OSA & 102 with OSA). [2]: Some cases had more than one condition. Values present as number & % were analyzed by Fisher's exact or chi-square tests. Values present as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.

Table 3. Sleep parameters and laboratory findings among the studied samples.

Variables		All cases n = 300	Without OSA n = 91	With OSA n = 209	P-value
Sleep efficiency	Mean ± SD Min - Max	74.3 ± 16.5 8.0 - 98.2	79.0 ± 14.7	72.2 ± 16.8	0.001*
AHI (event/H)	Mean ± SD Min - Max	24.4 ± 26.0 0 - 110	3.6 ± 3.3	33.5 ± 26.4	<0.001*
STOP-BANG score	Mean ± SD Min - Max	5.7 ± 1.6 1 - 8	3.9 ± 1.6	6.5 ± 0.9	<0.001*
Nadir O_2 sat%	Mean ± SD Min - Max	84.5 ± 10.5 71 - 96	91.7 ± 2.5	82.4 ± 11.1	<0.001*

AHI: Apnoea hypopnea index. Values present as mean ± SD were analyzed by Mann-Whitney *U* test. *: Significant.

(83.3%) of patients with T2DM and OSA suffered from HTN with increasing severity of both HTN and T2DM (as indicated by the number of medications received) compared to subjects who have diabetes without OSA (Table 4).

Variables that showed significant differences in the initial analysis were further evaluated according to the degree of severity of OSA. Increasing age, BMI, AHI, STOP-BANG score, HBA1C, and presence of HTN or DM were found to be significantly associated with increased severity of OSA. Decreasing sleep efficiency or Nadir O2% saturation was found to be significantly associated with increased severity of OSA. The severity of both HTN and T2DM (as indicated by

Table 4. Different parameters among diabetic patients with and without OSA.

Variables		All diabetic cases n = 98	Diabetic without OSA n = 20	Diabetic with OSA n = 78	P-value
Age (years)	Mean ± SD Min - Max	48.2 ± 12.9 36 - 78	45.8 ± 13.4	51.4 ± 12.8	0.087
Gender	Male	53 (54.1)	11 (55.0)	42 (53.8)	0.926
	Female	45 (45.9)	9 (45.0)	36 (46.2)	
BMI (kg/m^2)	Mean ± SD Min - Max	38.5 ± 7.7 33.1 - 51.7	36.0 ± 8.1	40.1 ± 7.5	0.034*
HTN		75 (76.5)	10 (50.0)	65 (83.3)	0.002*
Severity of HTN (n = 75)	Monotherapy		5 (50.0)	10 (15.4)	0.035*
	2-line therapy		3 (30.0)	26 (40.0)	
	≥3-line therapy		2 (20.0)	29 (44.6)	
Severity of T2DM (n = 98)	Monotherapy		11 (55.0)	20 (25.6)	0.033*
	2-line therapy		5 (25.0)	24 (30.8)	
	≥3-line therapy		4 (20.0)	34 (43.6)	
AHI (event/H)	Mean ± SD Min - Max	26.5 ± 22.7 0 - 110	3.9 ± 3.1	34.2 ± 23.0	<0.001*
Nadir O_2 sat%	Mean ± SD Min - Max	88.8 ± 11.5 74 - 96	91.1 ± 3.7	85.4 ± 10.8	0.023*
HBA1C	Mean ± SD Min - Max	8.0 ± 1.5 5.2 - 11.5	7.1 ± 1.6	8.5 ± 1.4	0.001*
STOP-BANG score	Mean ± SD Min - Max	5.7 ± 1.6 1 - 8	5.2 ± 1.3	6.3 ± 1.3	0.001*

BMI: Body mass index, HTN: Hypertension, T2DM: Type 2 diabetes mellitus, AHI: Apnoea hypopnea index, HBA1C: Glycated hemoglobin A. Values present as number & % were analyzed by Fisher's exact or chi-square tests. Values present as mean ± SD were analyzed by Mann-Whitney U test. *: Significant.

the number of medications received) was significantly higher with increasing severity of OSA (Table 5).

4. Discussion

Obesity is rising globally and the associated comorbidities like OSA and T2DM are also increasing globally [23]. OSA is one of the major risk factors linked to HTN, T2DM, metabolic syndrome, and cardiovascular diseases [24].

The association between OSA and insulin resistance and diabetes are still unclear. Use of CPAP can reverse insulin resistance. Sleep fragmentation, sleep deprivation, and hypoxemia (which all occur in OSA) are thought to play independent roles in glucose intolerance. Conflicting results show that reversal of glucose intolerance may occur when OSA is treated. There is increasing evidence that supports the role of OSA in exacerbating insulin control in patients with T2DM. This was found as an effect independent of adiposity and other confounders [25].

Table 5. Relation between the severity of obstructive sleep apnea and different study variables.

Variables		Non-OSA n = 91	Mild n = 76	Moderate n = 57	Severe n = 76	P-value
Age (years)		41.7 ± 14.0	51.2 ± 11.7	53.4 ± 12.5	55.7 ± 11.2	<0.001*
BMI (kg/m²)		33.9 ± 7.6	35.1 ± 7.0	38.5 ± 8.8	41.2 ± 6.9	<0.001*
HTN		24 (26.4)	22 (28.9)	23 (40.4)	57 (75.0)	0.013*
Severity of HTN[1] (n = 126)	Monotherapy	12 (50.0)	8 (36.4)	6 (26.1)	8 (14.0)	0.037*
	2-line therapy	7 (29.2)	8 (36.4)	9 (39.1)	22 (38.6)	
	≥3-line therapy	5 (20.8)	6 (27.3)	8 (34.8)	27 (47.4)	
T2DM		20 (22.0)	24 (31.6)	20 (35.1)	34 (44.7)	0.040*
Severity of T2DM[2] (n = 98)	Monotherapy	11 (55.0)	11 (45.8)	5 (25.0)	4 (11.8)	0.017*
	2-line therapy	5 (25.0)	7 (29.2)	6 (30.0)	11 (32.4)	
	≥3-line therapy	4 (20.0)	6 (25.0)	9 (45.0)	19 (55.9)	
Sleep efficiency		79.0 ± 14.7	75.1 ± 16.5	71.8 ± 15.8	69.6 ± 17.6	0.022*
AHI (event/H)		3.6 ± 3.3	12.5 ± 8.0	22.0 ± 4.5	54.0 ± 20.1	<0.001*
STOP-BANG score		3.9 ± 1.6	6.2 ± 0.8	6.4 ± 0.8	6.8 ± 0.8	<0.001*
Nadir O_2 sat%		91.7 ± 2.5	87.0 ± 4.3	82.5 ± 7.7	74.9 ± 14.2	<0.001*
HBA1C[2] for patients with T2DM		7.1 ± 1.6	8.1 ± 1.5	8.5 ± 1.5	8.7 ± 1.2	0.004*

BMI: Body mass index, HTN: Hypertension, T2DM: Type 2 diabetes mellitus, AHI: apnea hypopnea index, HBA1C: Glycated hemoglobin A. [1]: Only among HTN cases (n = 126; 24 without OSA, 22 mild, 23 moderate & 57 severe OSA). [2]: Only among T2DM cases (n = 98; 20 without OSA, 24 mild, 20 moderate & 34 severe OSA). Values present as number & % were analyzed by chi-square test. Values present as mean ± SD were analyzed by Kruskal-Wallis test. *: Significant.

The main purpose of this study was to explore the relation between the severity of OSA and the severity of T2DM and HTN. Patients were evaluated with PSG based on a combination of symptoms and risk factors indicative of OSA, including daytime snoring, sleepiness, and obesity. In our study, 69.7% were diagnosed with OSA, among them. T2DM and HTN were present in 37.3% and 48.8%, respectively.

These findings agreed with Alshehri *et al.* who found 74.8% of Saudi patients were diagnosed with OSA with male had a significantly higher prevalence of OSA and mean AHI than female [26]. Wali *et al.* found that 67.9% of Saudi population had OSA. History of HTN and T2DM were present in 9.9% and 8.1% in non-OSA group and 22.6% and 13.6% in OSA group, and they considered HTN and T2DM as significant risk factors associated with OSA [27]. In the same context, Kalakattawi *et al.* studied a total of 197 diabetic patients with OSA and found that the prevalence of HTN was 35%, which was less than that of our participants (83.3%) [28]. Sweed *et al.* studied 244 patients and found 62% had severe and very severe OSA. Among these patients, 68% had HTN and 50% had DM [29].

In this study, the mean STOP-BANG score (5.7 ± 1.6) was significantly higher

among patients with OSA and the score increased with increasing severity of OSA. Diabetics with OSA had significantly higher score (6.3 ± 1.3) than diabetics without OSA (5.2 ± 1.3). These findings disagreed with Kalakattawi *et al*. who found the mean STOP-BANG score was 2.6 ± 1.7 [28]. In our study we confirmed OSA by sleep study while Kalakattawi *et al*. used STOP BANG score as a predictor without confirmation of OSA.

Among patients with diabetes in our study, those with OSA had significantly higher BMI, AHI, HBA1c, and STOP-BANG scores and significantly lower Nadir O_2 saturation % than those without OSA. Majority (83.3%) of patients with diabetes with OSA suffered from HTN with increasing severity of both HTN and T2DM (as indicated by the number of medications received) than those without OSA.

This is in agreement with Embarak *et al*. who studied 110 Egyptian patients by PSG and found that 60% had OSA. They also observed that patients with OSA had longer duration of diabetes and higher systolic BP and used oral hypoglycemic and insulin more frequently than patients without OSA [30].

Systemic HTN is observed in 50% - 70% of patients with OSA. Several large cross-sectional studies have demonstrated that OSA is a risk factor for developing HTN, independent of obesity, age, alcohol intake, and smoking [25].

A recent review estimated that up to 70% of patients with T2DM have comorbid OSA, and that 15% - 30% of patients with OSA present T2DM [9]. Whether untreated OSA has deleterious effects on glucose control in patients with T2DM is a crucial issue that has been addressed by several recent studies [31] [8].

In this study, among patients with diabetes, HBAIC was higher among OSA versus non-OSA and higher levels of HBAIC were linked to the severity of OSA (HBAIC: 7.1 ± 1.6 in non-OSA, 8.1 ± 1.5 in mild, 8.5 ± 1.5 in moderate and 8.7 ± 1.2 in severe OSA). This is in agreement with Kalakattawi *et al*. who found HBAIC was higher among diabetic with OSA versus non-OSA (8.6 ± 2.0 vs 6.7 ± 1.7) and diabetic group with high risk for OSA were using more drugs for diabetic control than diabetic group with low risk for OSA [28]. Similarly, our findings were in agreement with Kent *et al*. who studied 6616 patients from the ESADA cohort study undergoing sleep recording for suspected OSA, of whom 17.2% had comorbid T2DM. In 60 patients with diabetes, 46 of whom had OSA on PSG (mean AHI = 19.2). They concluded that diabetic subjects with more severe OSA had poorer glucose control [32]. An independent association between increased OSA severity and poorer glucose control was concluded by Aronsohn *et al*. and they considered this to be comparable to that of widely used hypoglycemic drugs [8]. On the other hand, other studies found no link between OSA and HbA1c [33] [34].

5. Study Limitations

First: the retrospective design using a database tool is subject to intrinsic biases and limitations including: it cannot determine causation, only association, inac-

curate coding, has lower level of evidence compared with prospective studies, misdiagnosis, pilot trial was not performed, inability to track disease change over time, variability between providers and subjected to unmeasured confounding. Second: the relation between OSA and diabetes-related complications at different BP levels was not considered. Third: the compliance with antidiabetic and antihypertensive drugs was not available. Fourth: the effects of some important risk factors for diabetes and HTN like family history and physical activity could not be accurately determined. Fifth: Follow up of cases and outcome after initiating OSA treatment was not assessed. Lastly: we used a patient sample referred to a sleep disorders center, instead of a general population sample.

6. Conclusion

There is a relation between OSA and T2DM and HTN. Risk of OSA is higher among patients with uncontrolled T2DM and HTN. OSA should be suspected in subjects with obesity, especially with uncontrolled HTN and T2DM.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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