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# Metabolic Control and Disease Complications in Type 2 Diabetes as a Function of Obstructive Sleep Apnea Syndrome Severity

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## Abstract

**Background:** Obstructive Sleep Apnea Syndrome (OSA) is a disabling condition displaying strongly associated with cardiovascular complications in Type 2 diabetes (T2DM). Therefore, OSA treatment is a compelling, yet not consistently successful task requiring lifestyle adaptations, bariatric surgery and mechanical device utilization, yet new anti-hyperglycemic drugs, i.e., sodium-glucose co-transporter 2 inhibitors (SGLT2-is) and Glucagon-like peptide-1 receptor agonists (GLP1-ras) could also help. We aimed to assess OSA prevalence and association with metabolic control and complications in T2DM patients on different treatment schedules.

**Methods:** this retrospective study involved 3870 T2DM adults consecutively referring to our outpatient wards, polysomnographycally tested for apnea/hypopnea index (AHI) evaluation and divided into controls and mild (AHI 6-30 events/hour) or severe OSA (≥30 events/hour) groups.

**Results:** besides confirming the reported high OSA rate and close association with BMI, poor glucose control and cardiovascular complications, we also described increasing OSA severity with the rate and severity of T2DM metabolic derangement and comorbidities.

**Conclusion:** T2DM patients must be tested and eventually treated for OSA to attain better metabolic outcomes and reduce/prevent long-term complications. Whether SGLT2-is and GLP1-ras may prove successful per se or as an add-on to current treatment tools requires further investigation, possibly through dedicated clinical trials.

**Keywords:** Sleep Disorders; Obstructive Sleep Apnea; Type 2 Diabetes; Obesity; New Anti-Hyperglycemic drugs

## Abbreviations

OSA: Obstructive Sleep Apnea; T2DM: Type 2 Diabetes; SGLT2: Sodium-Glucose Co-Transporter 2; GLP1-Ras: Glucagon-Like Peptide-1 Receptor Agonists; AHI: Apnea Hypopnea Index; AHEAD: Action for Health in Diabetes; CAN: Cardiac Autonomic Neuropathy.

## Introduction

Obstructive Sleep Apnea Syndrome (OSA) is a frequent, severe, disabling sleep disorder. OSA mainly affects people with obesity, type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia and is strongly associated with cardiovascular complications [1]. As from the bidirectional relationship between T2DM and OSA, the latter represents a risk factor for the former and, vice versa, people with T2DM have a high risk of OSA.

Several studies described increased glucose levels and insulin resistance in patients with OSA [2] and, according to the Sleep Action for Health in Diabetes (AHEAD), 30% of people with T2DM and obesity suffer from OSA, thus accounting for several times higher prevalence than the general population [3,4].

The Sleep Heart Health Study enrolling 2000 patients pointed to a 1.44 odds ratio for abnormal glucose tolerance among patients with an Apnea Hypopnea Index (AHI) ≥ 15 compared to people with lower AHI levels. It also confirmed findings from the Nurse's Health Study suggesting the development or exacerbation of T2DM due to curtailed sleep duration due to OAA-associated sleep fragmentation [5,6]. On the other hand, compared with those sleeping 7-8 hours per night, individuals with ≤5- or <6-hour-sleep per night displayed adjusted odds ratios for T2DM of 2.51 (95% CI, 1.57 – 4.02) and 1.66 (95% CI, 1.15 – 2.39), respectively.

All the above-mentioned phenomena explain why, based on quantitative and validated measures, the prevalence of polysomnographically diagnosed OSA is higher in people with prediabetes and T2DM assessed by fasting glucose levels or glucose tolerance tests than in the general population, ranging from 18% in primary care [7] to 58% in an older cohort [8] and even to 86% in T2DM with obesity patients [9]. In addition, T2DM seems to increase the likelihood of OSA [8] through autonomic and central nervous system dysfunction.

Several cross-sectional studies have found a detrimental impact of OSA on glucose control in type 2 diabetes [10-13]. According to Aronsohn RS, et al. [12], who studied 60 people with type 2 diabetes, polysomnography-derived AHI positively correlated with HbA1c after controlling for multiple confounders, and the effect size of AHI on HbA1c was more relevant than that of some hypoglycemic drugs. However, possibly because of the high prevalence of older participants with obesity and a longer duration of diabetes, the investigators of a subanalysis of a large prospective study involving 305 of 5,145 participants from 4 of 16 centers could not confirm such correlation and only found some between fasting glucose and sleep efficiency [14]. In contrast, despite showing a significant HbA1c predicting ability for AHI in glucose-intolerant patients, others found a stronger inverse correlation between oxygen saturation and Hba1c in people with T2DM [15]. When taken together, all of the above shows that, in T2DM, moderate to severe OSA associates with poor metabolic control.

Prompted by such observations, we conducted a retrospective analysis of the data archived in the electronic records of a large outpatient cohort of people with Type 2 diabetes mellitus (T2DM) to evaluate the rate of altered incidence of apnea/hypopnea (AHI) events and its possible relationships with clinical parameters and metabolic control.

## Subjects and Methods

Initially, we selected 4300 subjects with T2DM over 18 years of age consecutively referring to our outpatient wards all participants providing written informed consent to use their anonymized data for research purposes and undergoing polysomnography for apnea/hypopnea index (AHI) evaluation. After excluding from the analysis those whose recordings dated over six months before the study or with active neoplasms, chronic inflammatory organ diseases, neurological, psychiatric diseases, cognitive defects, or requiring continuous caregiver assistance for broncho-pulmonary and oro-pharyngeal diseases, we ended up with the final selection of 3870 participants. We considered all participants with an AHI greater than 5 events/hour to suffer from sleep apnea (OSA) and a severe form of OSA if the AHI was greater than 30 events/hour (Figure 1).

Continuous variables were expressed as mean ± SD. The Wilcoxon signed-ranks test and the Mann–Whitney U-test were used to compare groups as needed. Multiple regression analysis was performed for the objective variable, as seen in Tables 1 and 2, and p values less< 0.05 were considered significant. All statistical analyses were conducted using the SAS Program (Release 9.4, SAS Institute, Cary, NC, USA). This study was reviewed and approved by the Scientific Committee of Nefrocenter Research Network (protocol n.65/2024, on 17 November 2024).

## Results

Figure 1 shows the enrollment flowchart. The subjects meeting the inclusion criteria were divided into three groups

based on the presence and severity of respiratory disorders: (i) Group A, n=2734 control participants (70.7% of those enrolled), accounted for those without sleep or nocturnal breathing disorders (AHI < 5/hour); (ii) Group B, n=887 OSA-affected participants with Hypopnea (78.1% of the total class with AHI >5/hour), accounted for by those with AHI >5 and < 30/hour; (iii) Group C, n=249 OSA-affected participants with severe Apnea (21.9% of all participants with AHI > 5/hour), who had an AHI >30/hour.

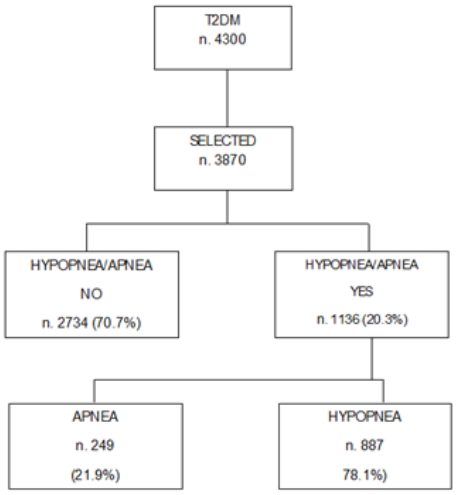


**Figure 1:** Flow chart of the enrolment procedure.

The general characteristics of the study population are described in Table 1, showing that the three groups had a similar M/F ratio and an equally similar rate of GLP-1ra, SGLT-1is and other oral hypoglycemic agent utilization.

| | APNEA/HYPOPNEA INDEX | | |
|---|---|---|---|
| | **Group A** | **Group B** | **Group C** |
| | **< 5/hour** | **≥ 5 < 30/hour** | **≥30/hour** |
| Sample size (n) | 2734 | 887 | 249 |
| Sex (M/F) | 1435/1299 | 498/389 | 148/101 |
| | 1.1 | 1.28 | 1.47 |
| Age (years) | 58.2±5.3 | 62.4±3.6 | 64.2±4.2* |
| | (52-67) | (55-69) | (59-71) |
| Diabetes duration (years) | 8±3.1 | 10±5.2 | 14±6.4 |
| | (4-12) | (4-17) | (7-23) |
| HbA1c (%) | 7.2±1.4 | 7.6±2.1 | 8.2±1.4** ° |
| | (6.6-7.3) | (7.2-8.1) | (7.6-9.8) |
| BMI (kg/m2) | 28.2±2.4 | 29.9±2.2 | 34.2±2.5 ** ° |
| | (25.231.4) | (27.1-33.4) | (28.1-38.4) |
| FPG (mg/dl) | 137.5±20.2 | 147.2±21.8 | 162.3±31.7 ** ° |
| | (109±169) | (125-198) | (171-258) |
| Creatinine (mg/dl) | 0.89±0.57 | 1.09±0.55 | 1.41±0.62 ** ° |
| | (0.76 – 1.26) | (0,89 – 1.99) | (1.10 – 2.09) |
| eGFR (ml/min/1.73m2)& | 81.7±12.9 | 70.4±10.4 | 54.5±14.8 ** ° |
| | (73.5 – 109.8) | (57.3 – 81.4 | (32.4 - 72.6) |

| | | | |
|---|---|---|---|
| Total Cholesterol (mg/dl) | 189±24 | 219±31** | 249±34 ** ° |
| | (174-224) | (181-234) | (197-278) |
| HDL-Cholesterol (mg/dl) | 42±6 | 40±4 | 37±4* |
| | (32-46) | (30-45) | (28-40) |
| Triglycerides (mg/dl) | 159±18 | 166±24 | 221±27 ** °° |
| | (131-179) | (139-198) | (167-298) |
| LDL-Cholesterol | 102±19 | 116±34 | 136±31 ** °° |
| | (89-207) | (97-243) | (119-189) |
| Insulin Treatment n. (%) | 328 (12) | 222 (25) * | 102 (41) ** ° |
| GLP-1ra n. (%) | 492 (18) | 133 (15) | 50 (20) |
| SGLT-2isn. (%) | 438 (16) | 177 (20) | 45 (18) |
| Other hypoglycemic drugs n. (%) | 1476 (54) | 355 (40) | 52 (21) |
| **p<0.01 vs A; *p <0.05 vs A; °° p<0.01 vs B; ° p<0.05 vs B | | | |
| (&) CKD-EPI sec. Levey AS, et al. CKD-EPI. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009 May 5;150(9):604-12. | | | |

**Table 1:** General characteristics of participants. Data are expressed as M±SD with range in brackets or number of participants with % in brackets.

Conversely, moving from Group A to Group C, they displayed a progressive increase not only in age (58.2±5.3 yrs, 62.4±3.6 yrs, 64.2±4.2 yrs, respectively), which reached significance only between groups C and A (p<0.05), but also in BMI (28.2±2.4 kg/m,2 29.9±2.2 kg/m2 and 34.2±2.5 kg/m2, respectively; see Fig. 2), HbA1c (7.2±1.4%, 7.6±2.1%, and 8.2 ±1.4%, respectively; see Fig. 3), fasting glycemia (FPG) (137.5±20.2 mg/dl, 147.2±21.8 mg/dl, and 162.3±31.7mg/dl, respectively), serum creatinine (1.89±0.24mg/dl [range1.74-2.24],1.09±0.55mg/dl [range 0.89–1.99], and 1.41±0.62 mg/dl [range 1.10 – 2.09], respectively), eGFR (81.7±12.9 ml/min/1.73m2 [range 73.5 – 109.8]) 70.4±10.4 ml/min/1.73m2 [range 57.3 – 81.4] and 54.5±14.8 ml/min/1.73m2 [range 32.4 - 72.6], respectively), all of which invariably reaching significance in group C vs. A (p<0.01) and vs. B (p<0.05). Similar phenomena were observed for insulin treatment (12%, 25%, and 41%, respectively) with significant differences between Groups B and A (p<0.05) and between Group C and the other two (p<0.01 vs. A, and p<0.05 vs. B; see fig. 4); HDL-Cholesterol (42±6 mg/dl, 40±4mg/dl and 37±4 mg/dl, respectively) with significant differences between Groups C and A (p<0.05) and for the other lipid parameters, i.e., triglycerides (159±18 mg/dl, 166±24 mg/dl and 221±27 mg/dl, respectively) with significant differences between Groups C and the other two (p<0.01 vs. A, and p <0.05 vs. B), total cholesterol (189±24 mg/dl, 219±31 mg/dl and 249±34 mg/dl, respectively) and LDL-Cholesterol (102±19 mg/dl, 116±34 mg/dl and 136±31 mg/dl, respectively) with significant differences between Groups C and the other two as well (p<0.01 vs. A and B).

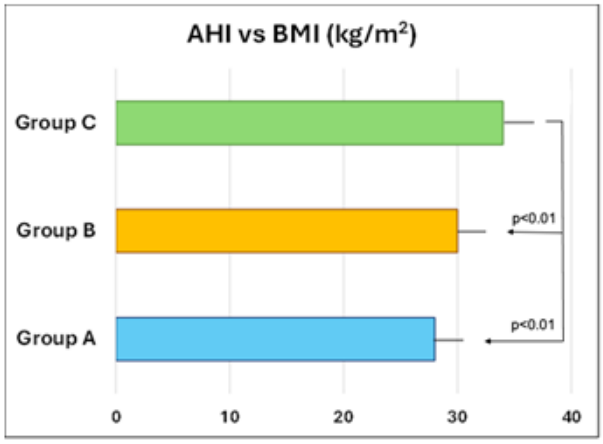


**Figure 2:** Distribution of mean BMI (kg/m2) levels and significance of relative differences among the three AHI groups.

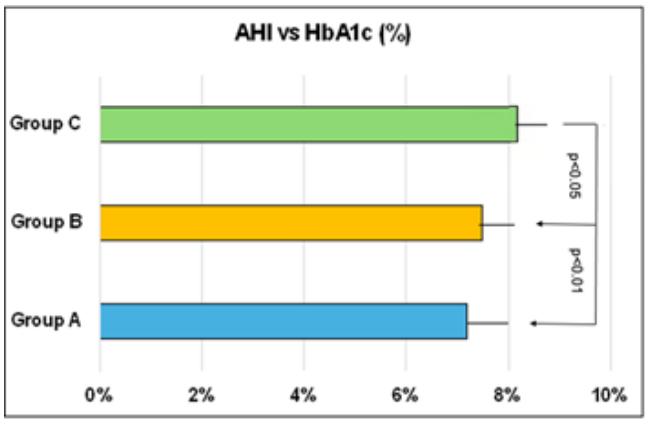


**Figure 3:** Distribution of mean HbA1c levels and significance of relative differences among the three AHI groups.

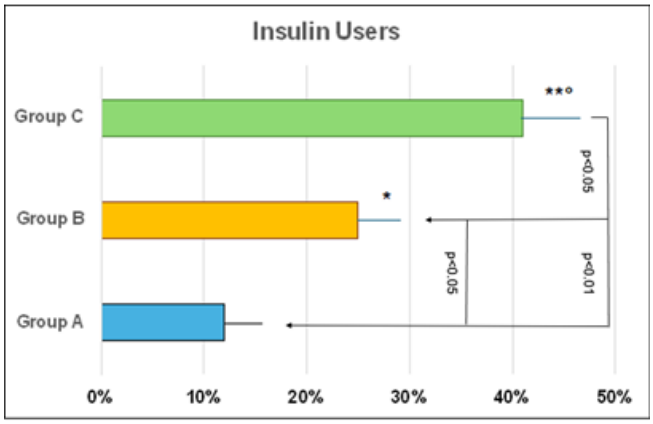


**Figure 4:** Distribution of mean percent insulin users and significance of relative differences among the three AHI groups.

Table 2 shows the rate of comorbidities, including arterial hypertension, dyslipidemia, micro- and macrovascular complications: they were all progressively increasing from Group A to Groups B and C with invariably significant differences between the two degrees of OSA severity and between each of them and controls (Table 2).

| | Group A | Group B | Group C |
|---|---|---|---|
| Hypertension | 37.3 | 42.6* | 62.4**°° |
| Dyslipidemia | 52.5 | 66.3** | 78.6**° |
| Coronary Heart Disease | 9.2 | 25.6** | 57.8*° |
| Central/Peripheral Angioplasty | 3.2 | 16.4** | 44.5**°° |
| Stroke | 6.3 | 19.5* | 37.4**°° |
| Peripheral Artery Disease | 9.4 | 27.1* | 42.7**°° |
| Foot Ulcer | 1.1 | 4.3** | 10.2**°° |
| Retinopathy | 16.7 | 24.3** | 42.7**°° |
| Maculopathy | 4.2 | 7.3** | 12.9**°° |
| Chronic Kidney Disease | 6.8 | 24.7** | 43.9**°° |

| | | | |
|---|---|---|---|
| Peripheral Neuropathy | 18.4 | 23.5* | 36.9**°° |
| Autonomic Neuropathy | 5.6 | 12.8** | 19.7**° |
| **p<0,01 vs A; °°p<0.01 vs B; *p<0.05 vs A; ° p<0.05 vs B | | | |

**Table 2:** Comparison and significance of between-group differences observed for the percent rate of comorbidities and complications.

All chemical and clinical variables were evaluated with univariate analysis. The significant ones then entered multivariate analysis to compare controls with cumulatively considered OSA participants, as reported in Table 3.

| | Odds Ratio | 95% Confidence Interval | p |
|---|---|---|---|
| Age | 0.77 | 0.24 – 1.91 | n.s. |
| BMI | 4.28 | 2.16 – 8.27 | < 0.001 |
| HbA1c | 1.98 | 1.62 – 3.16 | < 0.001 |
| Insulin therapy | 1.07 | 0.78 – 1 26 | n.s. |
| Other hypoglycemic agents | 0.98 | 0.68 – 1 57 | n.s. |
| Lipid lowering Agents | 0.87 | 0.66 – 1 75 | n.s. |
| Antihypertensive Drugs | 1.27 | 0.77 – 1.93 | n.s. |
| Retinopathy | 2.12 | (1.26 – 4.89) | <0.001 |
| Chronic Kidney Disease | 3.39 | (1.98 – 5.47) | <0.001 |
| Maculopathy | 1.78 | 1.08 – 2.73 | <0.001 |
| Peripheral/aAutonomic Neuropathy | 1.28 | 0.87 – 2.11 | n.s. |
| Peripheral Artery Diseaase | 1.21 | 0.74 -3.02 | n.s. |
| Coronary Heart Disease | 3.16 | 1.87 – 6.23 | <0.001 |
| Central/Peripheral Angioplasty | 1.38 | 0.98 – 3-87 | n.s. |
| Stroke | 1.12 | 0.87 – 2.29 | n.s. |

**Table 3:** Results of the multivariate analysis of all participants with and without OSA for parameters found to reach significance at the univariate analysis.

Through multivariate analysis, age (OR 0.77, 95% CI 0.24-1.91), hypoglycemic (OR 0.98, 95% CI 0.68 – 1.57), lipid-lowering (OR 0.87, CI 95% 0.66 – 1.75), antihypertensive drug utilization (OR 1.27, CI 95% 0.77 - 1.93), as well as percent insulin treatment (OR 1.98, CI% 0.62 - 3.16) and the rate of peripheral artery disease (OR 1.21, CI 95% 0.74 -3.02), central /peripheral angioplasty (OR 1.38, CI 95% 0.98 – 3.87), stroke (OR 1.12, 95% CI 0.87 – 2.29) and peripheral/autonomic neuropathy (OR 1.28, 95% CI 0.87 – 2.11) did not appear to influence the results significantly.

A high level of significance was witnessed, instead, for BMI (OR 4.28, 95% CI 2.16 – 8.27), HbA1c (OR, 1.98 95% CI 0.62 – 3.16), coronary heart disease (OR 3.16, 95% CI 1.87 – 6.23); diabetic retinopathy (OR 2.12, 95% CI 1.26 – 4.89); maculopathy (OR 1.78, 95% CI 1.08 – 2.73), and chronic kidney disease (OR 3.39, 95% CI 1.98 – 5.47).

## Discussion

The analysis of the data collected suggested the following. Sleep apnea syndrome is widespread in people with diabetes mellitus and insulin resistance, as widely documented in the literature [5,6,16], is closely linked to obesity [3,17-19] and increases the risk for cardiovascular events, including heart failure [20-24] and stroke [23] and is burdened by a high risk of mortality [4,25].

Our data confirm a close association of OSA with BMI, the frequency of which seems to grow in parallel with the progression of OSA severity, as documented by the progressively increasing BMI mean level observed from

Group A to Group C.

In agreement with other papers, OSA's association with glycemic control is also confirmed by the progressive HbA1c level increase from Group A to Group C [14,26]. Conversely, probably due to differences in other authors' case sampling and number, we could not detect any differences in gender or age [27].

Even the increasing frequency of cardiovascular and atherosclerotic events we recorded in the classes of increasing severity of OSA participants is in agreement with the literature data [5,23,24,28-30], a phenomenon probably linked to high levels of circulating lipids and inflammation markers typically linked to diabetes and obesity [31-35].

Regarding the microvascular complications of diabetes, again, our results agree with the literature [36-40]. Indeed, we found a progressive, significant increase in the frequency of retinopathy and maculopathy with worsening OSA (16.7% and 4.2% in controls, 24.3% and 7.3% in participants with an AHI between 5 and 30 apneas/hour, and 42.7and 12.9% % in those with an AHI higher at 30/hour, respectively). The significant difference between controls and cumulatively considered OSA participants was validated by multivariate analysis (OR 2.12 and 1.78, respectively). Similar behavior was observed for chronic kidney disease, with the frequency of affected participants significantly increasing as the clinical picture worsened, with 6.8% of affected participants in the control group, 24.7% in the medium severity OSA group and 43.9% in the more severe OSA group. This data agreed with the literature and, in our series, was also validated through an OR of 3.39 at multivariate analysis.

In agreement with what was reported by other authors [38,41,42], we could also detect significant differences among the three groups for autonomic and, more impressively, peripheral neuropathy (see Table 2), although, probably due to the relatively small series size, when comparing participants with and without OSA, multivariate analysis failed to confirm such significance (Table 3).

Unfortunately, we were unable to find significant correlations between OSA symptoms and SGLT-2i- and GLP-1ra-administration, likely due to the limited number of participants on that specific treatment. Therefopre, a more in-depth analysis of this issue is necessary, especially for the lack of other effective drugs for the prevention and pharmacological treatment of OSA, many authors consider to represent the new therapeutic frontier for such a disabling disease.

Indeed, the beneficial effects of SGLT-2is on OSA may involve the following mechanisms [43]: (i) sympathetic activity inhibition [41,44], counteracting cardiac autonomic neuropathy (CAN), cardiovascular defects and renal dysfunction [42]; (ii) direct benefits on renal function [45] preventing CAN-from entering a renal dysfunction-related vicious circle [46,47]; (ii) increased Ht expected to reduce nocturnal hypoxia [48-50]. In addition, SGLT2is enhance lipolysis and fatty acid beta-oxidation and thus may prevent OSA by decreasing the amount of visceral and subcutaneous adipose tissue. Moreover, based on experimental and clinical evidence, they may avoid the onset and progression of NAFLD, whose prevalence exceeds 50% and, thus, exert further protective effects against heart failure with preserved ejection fraction in people with T2DM and OSA [51,52].

Some essential properties of GLP-1ra are linked to the combined effects on the significant reduction in body weight, cardio-renal protection, and the ability to reduce liver fat content [53-56]. As is evident from the literature, SGLT-2is and GLP-1ras have such properties as to positively affect the comorbidities and chronic complications associated with both T2DM and OSA and, therefore, they are expected to at least reduce, if not control, their impact.

Unfortunately, the limitations of our study, i.e., the retrospective nature, and the number of participants using SGLT-2i and GLP-1ras too low to grant a reliable investigation on the role of those innovative drugs and OSA, does not let us to provide specific indications. On the other hand, as insulin was much more utilized than all other hypoglycemic drugs in our participants with severe OSA (see Table 1), might reflect more severe beta-cell dysfunction, so that physicians were less motivated to use add-on SGLT-2is and GLP-1ras in the present treatment strategy context.

## Conclusion

Our study confirms the literature data on the high frequency of OSA in people with T2DM and the close association of OSA in the same participants with BMI, poor glucose control, and macro-/micro-vascular complications. However, our data introduce an element of novelty by also pointing to an increasing rate and severity of dysmetabolism, as reflected by high HbA1c and glucose levels, and comorbidities, including dyslipidemia, arterial hypertension, cardiac, macro-and microvascular complications with the increasing severity of OSA. So, T2DM patients must be tested and eventually treated for OSA to attain better metabolic outcomes and reduce/prevent long-term complications. Whether SGLT2-is and GLP1-ras may prove successful per se or as an add-on to current treatment tools requires further investigation through dedicated clinical trials.

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## Authorship

All named authors (Sandro Gentile, Vincenzo Maria Monda, Giuseppina Guarino, Ersilia Satta, Maria Chiarello, Giuseppe Caccavale, Edi Mattera, Raffaele Marfella, and Felice Strollo) meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article taking responsibility for the integrity of the work as a whole and gave their approval for this version to be published.

## Authorship Contributions

Sandro Gentile wrote the manuscript, Felice Strollo and Vincenzo Maria Monda critically revised the text. Giuseppina Guarino, Maria Chiarello, Giuseppe Cacavale, Edi Mattera, Raffaele Marfella and Ersilia Satta critically read and approved the paper. All authors contributed to bibliographic data acquisition, critically assessed the results, and approved the final text.

## Disclosures

Sandro Gentile, Vincenzo Maria Monda, Giuseppina Guarino, Ersilia Satta, Maria Chiarello, Giuseppe Caccavale. Edi Mattera, Raffaele Marfella, and Felice Strollo have no financial interests (no personal, financial, commercial, or academic conflicts of interest) to declare in relation to the present study.

## Compliance with Ethics Guidelines

This study does not consider data from directly observed diabetic patients and is limited to the analysis of data retrospectively surveyed from anonymized historical clinical records collected after informed written consent for research purposes.

## Data Availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.



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