Insulin use could increase the risk of obstructive sleep apnea in type 2 diabetes mellitus

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ABSTRACT

Background: Obstructive sleep apnea (OSA) is a common disorder that can increase cardiovascular risk in patients with type 2 diabetes mellitus (T2DM). Little is known about specific risk factors for OSA in patients with T2DM.

Objective: Identify variables associated with an increased risk of OSA in T2DM.

Setting: T2DM outpatient clinic.

Measurements: Sleep-T2DM relevant variables were stratified according to STOP-Bang questionnaire scores, in order to recognize OSA risk associations.

Results: Insulin use was directly related to a higher risk of OSA in T2DM outpatients: RP 1,86; IC 1,315- 2,649; p< 0,001.

Limitation: Cross-sectional study, OSA diagnosed by non-objective measures.

Conclusion: In T2DM, the use of insulin increased the chances of belonging to a group of patients with a higher risk of OSA. The cost-benefit of treatment with insulin should be compared with other options, in patients already with T2DM with an increased risk for OSA.

Abbreviations

OSA: Obstructive Sleep Apnea; T2DM: Diabetes Mellitus Type 2; RP: Prevalence Ratio; PHQ -9: Patient Health Questionnaire; mPSQI: Pittsburgh Sleep Quality Index; BMI: Body Mass Index; HbA1c: Glycohemoglobin; Q1/Q3: Quartil 1 and 3; MEQ: Morningness-Eveningness Questionnaire; TFEQ-21: Three Factor Questionnaire-21; IGF1: Insulin-like growth hormone; DM1: Diabetes mellitus type 11; GLP1: Peptídeo Glucagon-Like 1; SGLT2: Sodium Glucose Cotransporter 2

Introduction

Obstructive sleep apnea (OSA) is a very prevalent disease in patients with type 2 diabetes mellitus (T2DM) [1,2]. It is known that it can increase cardiovascular risk, by increasing refractoriness to systemic arterial hypertension treatment [3]. T2DM mortality is associated with cardiovascular diseases, such as coronary heart disease and stroke [4]. In a patient with T2DM, OSA is an additional risk factor for mortality. In recent years, the relationship between OSA and glycemic control received special attention [5]. These studies pointed that the more severe OSA is the greater the impact on glycemic control of patients with T2DM [5]. This data is relevant to understand how the sleep alterations in OSA can contribute to the microvascular complications of T2DM, which are strictly related to glycemic control. However, cardiovascular mortality of patients with T2DM is poorly explained by glycemic control. Therefore, the study of risk factors that interfere with OSA risk in patients with T2DM may have great relevance. In view of this, the present investigation proposes to look for particularities of patients with T2DMthat

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KEYWORDS

- obstructive sleep apnea
- type 2 diabetes mellitus
- insulin

could worsen OSA and, therefore, increase cardiovascular risk and mortality.

Methodology

The study received the approval of a Research Ethics Committee before starting. All participants signed an informed consent form in accordance with the Declaration of Helsinki. 97 patients diagnosed with T2DM, aged between 40 and 60 years (Age was limited as it is a risk factor for insulin use and risk of apnea), and were included. Exclusion criteria were: (1) age <40 or >60; (2) pregnancy; (3) recent glucocorticoid use (4) conditions that determined a glycohemoglobin target above 7% (end-stage renal disease, recent acute coronary syndrome) and (5) recent T2DM diagnosis (<1 year before). The STOP-Bang questionnaire score was utilized to separate participants into 2 categories: (a) OSA risk (score ≥ 3); and (b) no OSA risk (score <3). Excessive daytime sleepiness was assessed using the Brazilian version of the Epworth Sleepiness Scale [6,7]. Diet was examined with the Brazilian version of Stunkard and Messick´s Three-Factor Questionnaire 21 (TFEQ-21) [8]. Depressive symptoms were evaluated with the Patient Health Questionnaire (PHQ-9) [8]. Horne and Östberg's Morningness-Eveningness Questionnaire cutoff points followed the recommendations of Taillard Sleep quality was studied according to the modified Pittsburgh Sleep Quality Index (mPSQI) proposed by Knutson which consider sleep quality independently of sleep duration [9,10]. The weekly frequency of alcohol intake, nocturnal pain and nocturia were assessed by self-report. Physical activity was established according to the minutes of weekly physical exercise. The body mass index (BMI) was obtained by dividing weight in kilograms by height squared in centimeters. Glycohemoglobin (HbA1c) was obtained by high performance liquid chromatography. Quantitative variables were described by mean and standard deviation, when distribution was normal, and median (Q1; Q3) when distribution was not normal.

Normality of distribution was verified by the Shapiro Wilk test. Quantitative variables were described by absolute values and percentages. A log-binomial univariate OSA regression model was adjusted to assess which variables would be candidates for a multivariate log-binomial OSA regression model. Variables with p-value ≤ 0.200 in the univariate model were candidates for a multivariate model. Multivariate models were adjusted and the variable with the highest non-significant p value was removed until only variables with p values ≤ 0.05 remained. The significance level was 5%.

Results

141 T2DM patients were interviewed and 97 included (TABLE 1). Median age was 52 years, 28% were female, and 32% were insulin users. Median glycohemoglobin was 7.4%, close to adequate T2DM control (<7%). Average BMI was 30 ± 4.93, a morning chronotype was present in 45.4% of the patients, and OSA risk was detected in 56.7%, given a STOP-Bang questionnaire score ≥ 3.

Characteristics were analyzed in relation to prevalence in the group at risk for OSA, defined by STOP-Bang ≥ 3 (Table 1). We present the results of this analysis how prevalence ratios, confidence intervals, and p-values. Older age, more physical activity during the week, higher glycohemoglobin values, and use insulin were more prevalent in the OSA risk group. On the other hand, being female reduced the prevalence in the OSA risk group. To eliminate possible errors resulting from interference between correlated variables in the univariate analysis, we performed a multivariate analysis with all variables with a p value <0.2. TABLE 2 shows the variables that entered the multivariate analysis and step by step those that left the multivariate model because they lost statistical significance.

Finally, after completing the multivariate model, we noted in TABLE 3 that the use of insulin increases the prevalence in the OSA risk group (PR:1.86; 95% CI 1.315-2.649, p<0.001) and being female reduces this prevalence (PR: 0.429; 95% CI 0.297; 0.618, p<0.001).

TABLE 1: Univariate analysis comparing risk of OSA and no risk.

Variables	characteristics	OSA risk	95% CI PR	p-value
Age	52,00 (48,00; 59,00)	1,052	1,012; 1,093	0,010
Female	28 (59,8%)	0,483	0,341; 0,686	<0,001
Black	8 (8,2)	1,071	0,595; 1,928	0,818

Time since T2DM diagnosis (years)	7,00 (3,00; 10,00)	1,016	0,983; 1,050	0,358
Physical activity (minutes per week)	0,00 (0,00; 120,00)	1,001	1,000; 1,002	0,022
Insulin users	32(33,0%)	1,573	1,138; 2,174	0,006
Glycohemoglobin%	7,40 % (6,50; 8,90%)	1,142	1,043; 1,250	0,004
Alcohol users	39(40,2%)	1,659	1,181; 2,330	0,004
Smokers	11(11,3%)	0,782	0,399; 1,531	0,473
Family historyofT2DM	71(73,2%)	0,893	0,617; 1,292	0,547
Hypnotic medication users	11(11,3%)	1,140	0,702; 1,851	0,596
Caffeine daily dose (mg)	190,00 (95,00;285,00)	1,000	1,000; 1,001	0,067
Uncontrolled food (TFEQ-21) (%)	22,22(11,11; 45,59)	1,004	0,998; 1,010	0,245
Cognitive restraint (TFEQ-21) (%)	44,50 ± 21,39	0,995	0,986; 1,004	0,256
Emotional nutrition (TFEQ-21) (%)	16,67(0,00; 44,44)	1,000	0,994; 1,006	0,950
Depressive symptoms score (PHQ-9)	10,00(5,00; 15,00)	1,014	0,990; 1,039	0,259
Chronotype score (MEQ)	64,00 (59,00; 69,00)	1,000	0,982; 1,019	0,977
Chronotypes-N (%) Intermediate Morning Evening	42(43,3) 44(45,4) 11(11,3)	1,034 0,795	0,722; 1,481 0,396; 1,599	0,855 0,521
BMI	30,99 ± 4,93	1,017	0,985; 1,050	0,295
STOP-Bang questionnaire score OSA risk absent (<3) OSA risk present (≥ 3)	42(43,3%) 55(56,7%)	-	-	-

TABLE 2. Multivariate analysis, step by step.

Variables	Model 1	Model 2	Model3	Model4	Model 5	Model 6
Age (p-value)	0,125	0,124	0,115	0,085	0,059	-
Female gender (p-value)	0,002	0,001	<0,001	<0,001	<0,001	<0,001
Physical activity (p- value)	0,177	0,230	0,236	-	-	-
Insulin user (p-value)	0,041	0,016	0,007	0,010	0,001	<0,001
Alcohol users (p-value)	0,258	0,389	-	-	-	-
Glicohemoglobin (p- value)	0,103	0,103	0,140	0,171	-	-
Caffeine daily dose (mg/ day) (p-value)	0,382	-	-	-	-	-
1,017	1,017	1,017	1,017	1,017	1,017	1,017

TABLE 3. Multivariate model final.

Gender **Male** **Female**	**Reference** **0,429**	**0,297; 0,618**	**<0,001**
Insulin user yes no	1,866 Reference	1,315; 2,649	<0,001

Discussion

Our work showed that the T2DM group that used insulin had a greater chance of belonging to the group at risk for OSA. This result admits several pathophysiological explanations and plausible practical implications for clinicians working with T2DM on a daily basis. It is known that T2DM patients who use insulin tend to gain weight with treatment [11]. This could be an explanation for a higher score in the STOP-Bang questionnaire, which presents BMI as one of its items. Our study, however, did not identify a weight difference between groups with and without OSA risk. A possible explanation for our finding would be the fact that insulin could increase body fat, without necessarily increasing body weight [12]. An increase in fat deposition in parapharyngeal fat pads, pharyngeal muscles, and genioglossus, unrelated to weight gain, would be a mechanism capable of increasing the risk of OSA among insulin users. This hypothesis is consistent with the findings of the study of Baukal, who identified an association between OSA, high insulin levels and increased body fat [13]. This could generate a cycle: insulin use, worsening of OSA, increased insulin resistance due to increased inflammatory markers secondary to intermittent hypoxemia and increased insulin doses for adequate glycemic control, feeding this insulin-OSA insulin cycle [12,14]. The higher prevalence of OSA in patients with type 1 diabetes mellitus (DM1) also reinforces a possible correlation between insulin and OSA. Banghoej found a high prevalence of OSAin patients with DM1 compared to patients without this disease. These patients have as mandatory treatment the use of insulin [15]. These patients have frequent episodes of hypoglycemia throughout life, which demonstrates that the dose of insulin used does not represent the physiological dose of this hormone. Although BMI is also a risk factor for OSA in patients with DM1, up to one third of these thin patients present with OSA. The association between insulin and worsening of diabetic neuropathy may also be a hypothesis to explain the higher risk association for OSA in T2DM patients using insulin. It has been shown that rapid changes in glycohemoglobin can lead to the progression of diabetic neuropathy [16]. Diabetic neuropathy could lead to autonomic dysfunction, reducing the central control of breathing and worsening the intrinsic muscle function of the larynx, leading to a greater tendency of these muscles to collapse, which would lead to a worsening of OSA [17]. Patients using insulin present a context of greater glycemic variability and, therefore, could present frequent triggers for the emergence of these central and peripheral mechanisms. Establishing lower glycemic variability in these patients could thus reduce the risk of OSA. The similarity of insulin to insulin-like growth hormone (IGF1) may also explain, from a pathophysiological point of view, the increased risk of OSA in patients with diabetes using insulin. This association may be analogous to what occurs in patients with acromegaly, in which higher levels of IGF1 are associated with a higher frequency of OSA [18]. In the same way that patients who use insulin could, due to mechanisms not yet understood, present a higher frequency of OSA. Until a decade ago, insulin was the only therapeutic option when available oral medications failed to control T2DM patients. Currently, however, there are a number of new medications to control T2DM. Many of these medications, such as GLP1 analogues and SGLT2 inhibitors, associate with weight and body fat reductions [19]. Previous studies have shown that both medications have benefits in terms of weight and OSA in these patients [20,21]. Despite the financial burden that such treatments impose, choosing these drugs instead of insulin might be cost-effective for selected groups of patients: obese subjects, patients already with OSA and those with a high risk score for OSA. Cost effectiveness would be obtained by the interruption of the insulin-OSA-insulin cycle. Two important negative outcomes for the T2DM patient would have been prevented: (1) the increase in macrovascular complications, initiated with the onset of insulin therapy precipitated OSA; and (2) the increase in microvascular complications, due to the lack of glycemic control generated by increasing needs for insulin in patients with more severe OSA. Some limitations can be pinpointed in this study. The work was cross-sectional, which hinders the establishment of causal links. We emphasize, however, that our dependent variable was the risk of OSA defined by the STOP-Bang questionnaire, which favors the direction of the insulin-only association. OSA diagnosis was not established by gold-standard polysomnography and OSA was estimated with the STOP-Bang questionnaire, which presents good sensitivity and specificity. Despite these criticisms, we emphasize that our work presents fundamental strengths when assessing the relationship between sleep and diabetes: the high number of variables included. This aspect assumes particular

relevancy, given that many confounding factors are present in sleep studies. Not only we analyzed several sleep related variables, but a choice was made for those connected to T2DM.

Conclusion

Our work, therefore, suggests an association between insulin use and OSA risk. It is interesting to point here that insulin should be used when necessary, but its use should be postponed in patients with OSA or at risk of OSA, when other options are available. In addition, we suggest that rapid control and sudden changes in blood glucose should be avoided. These measures can prevent the worsening of OSA in a patient with T2DM and the beginning of the insulin-OSA-insulin cycle and its vascular consequences. Finally, we think that the connection between insulin therapy and OSA requires further clarification with longitudinal studies, as it can be associated with increased cardiovascular mortality.

Declarations

■ Ethics approval and consent to participate

The study received the approval of a Research Ethics Committee before starting. All participants signed an informed consent form in accordance with the Declaration of Helsinki.

■ Consent for publication

The authors give full consent to the publication of this article

■ Availability of data and materials

Data from this work are available for submission upon request.

Compliance with Ethical Standards

■ Funding

This study received no funding

■ Conflict of interests

Author Wagner josé Martorina and Almir Tavares declares that he has no conflict of interest.

■ Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards

■ Informed consent

Informed consent was obtained from all individual participants included in the study.

■ Authors' contributions

The authors contributed in the elaboration of this work in an equivalent way

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