

Sleep apnea syndrome in diabetic patients

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Abstract: Sleep apnea syndrome (SAS) represents an important co-morbidity in diabetic patients that is frequently under-diagnosed. If left untreated, SAS significantly increases their morbidity and mortality. The aim of our study was to estimate the prevalence of SAS in diabetic subjects admitted in the clinical wards of the National Institute of Diabetes "NC Paulescu" and to identify clinical and laboratory parameters correlated with the presence of SAS. The study group comprised 101 diabetic subjects aged 22-81 years. Continuous nocturnal pulse oximetry was used in order to identify desaturation events suggestive of SAS. Overall 47.5% of patients presented with oxygen saturation patterns suggestive for SAS. The main predictors were age and weight, with the highest prevalence recorded in male subjects aged 50-69 years and with BMI 30-35 kg/m². Despite the fact that continuous nocturnal pulse oximetry is only a surrogate indicator for SAS, its low cost and simplicity allow its large scale use in order to identify subjects at high risk and their referral to specialized polysomnography centers.

Key Words: sleep apnea syndrome, diabetes, impaired driving.

The sleep apnea syndrome (SAS) is defined by the occurrence of loud snoring, witnessed breathing interruptions, or awakenings caused by gasping or choking in the presence of at least 5 obstructive respiratory events per hour, associated with daytime sleepiness [1]. Numerous data suggest that the sleep apnea syndrome (SAS) has a high prevalence in type 2 diabetes (T2DM) patients. There are millions of T2DM patients whose psychological or physical conditions are not recognized as induced by the presence of SAS.

Thus, every other diabetic patient has SAS and the vast majority of them are not yet diagnosed [2]. In addition, if left untreated, SAS represents an additional risk factor for cardiovascular morbidity in the general population but especially in diabetic patients [3,4]. In addition in diabetics, SAS aggravates insulin resistance and worsens their metabolic control as reflected by HbA1c [5], leading to an

increased prevalence of the chronic microvascular diabetic complications [6,7]. Interestingly, the presence of SAS increases also the risk for developing glucose metabolism disturbances, metabolic syndrome and overt T2DM [8,9].

Finally, the presence of SAS is associated with a high risk of acute respiratory failure and sudden death [10], situations with possible medico-legal implications.

The golden standard for the diagnosis of SAS is polysomnography [11]. However, polysomnography is a time-consuming and costly procedure. Continuous nocturnal pulse oximetry could be used as a surrogate diagnostic method for SAS, identifying obstructive apnea on the basis of the magnitude and frequency of recorded oxygen desaturation periods [12]. The pathognomonic aspect of "sawtooth wave" indicates the presence of cyclic regular desaturation periods and represents the graphical expression of the sleep obstructive respiratory anomalies

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characteristic for the SAS.

Sleep apnea is known to be associated with sudden death (and especially sudden infant death syndrome), increased aggressiveness, and increased risks for road traffic accidents.

Because of the high prevalence of the metabolic and respiratory pathology in the general population and the severity of the association between the two, we aimed to perform an observational study on a group of patients with this pathology in order to identify the most important predictive clinical and laboratory parameters, the associated risk factors as well as the possible correlations between the studied variables. The primary aim of the study was to identify the subjects with pulse oximetry patterns suggestive for SAS in a group of diabetic in-patients admitted in the 2nd Clinical Ward of the National Institute of Diabetes, Nutrition and Metabolic Diseases "Prof. NC Paulescu" from Bucharest. In addition, we aimed to study the possible correlation between clinical and laboratory parameters of these patients.

MATERIALS AND METHODS

The design of the study was observational, descriptive, and transversal, performed on a group of in-patients admitted in hospital between February and June 2011. The protocol of the study was approved by the local Ethics Committee and all subjects signed prior to inclusion an informed consent obtained according to the World Medical Association Declaration of Helsinki.

The study group included 101 diabetic patients, 58 Males (57.4%)/43 Females (42.6%), aged between 22 and 82 years (average 55.82, mode 58 years), with a diabetes duration between 1 and 36 years. The main inclusion criterion was the presence of diabetes and signing of the informed consent form.

In order to evaluate the possibility of SAS presence and identify the patients to be referred to a polysomnography center, we monitored the patients overnight using the pulse oximetry method that records the level of O₂ saturation in capillary blood. Pulse oximetry is the easiest and cheapest examination for SAS screening, easy to apply and interpret. It can be accepted for a diagnosis of SAS on the basis of magnitude and frequency of desaturation periods in a suggestive clinical context (snoring, apnea periods, described by the partner, agitated sleep, nocturnal sweating/polyuria, morning headache and daytime sleepiness).

The device used allowed the analysis and synthesis of all desaturation events. Using a special software, we could identify the typical sawtooth wave aspect of desaturation events associated with SAS (Figure 1). Interpretation of all pulse-oximetry recordings was made by a pneumologist specialized in sleep pathology.

Statistical analysis was performed using the Excel and SPSS software. Absolute, percentage and cumulative frequencies were calculated, testing for the differences between patients with or without SAS. Differences between median of the groups were studied using the Mann-Whitney test or the Student's t-test for differences between means. *Pearson's correlation coefficient* (r) was used to measure the strength of the association between two variables and its significance with t-distribution test.

RESULTS

47.5% of the patients had abnormalities of the pulse-oximetry recording suggestive for SAS. The study of the correlation between the presence of the SAS and the number of nocturnal desaturation events recorded by pulse-oximetry indicated the presence of a strong correlation (Spearman coefficient 0,719), statistically significant ($p = 0.01$). This result shows that there is a 99% probability that a high number of nocturnal desaturation events could be associated with the presence of SAS. 38,6% of cases showed a low number (1-5) of severe nocturnal desaturation events while 7.9% of patients had between 11 and 15 severe nocturnal desaturation events with more than 21 total events/night. 5 patients required intermittent oxygen therapy.

Regarding the severity of desaturation events, we calculated the oxygen desaturation index by dividing the number of desaturation events with O₂ level <90% to the total duration (hours) of observation. We found a strong correlation (Spearman coefficient 0.658) between the desaturation index and the presence of the SAS, indicating a 99% probability that a high desaturation index is associated with the presence of SAS.

In addition, we analyzed the most important clinical (age, sex, diabetes duration, diabetes type, Body Mass Index - BMI) and laboratory parameters (HbA1c, total cholesterol, HDL cholesterol, triglycerides, urea, creatinine, microalbuminuria, hemoglobin, uric acid, liver enzymes) comparatively in patients with or without SAS.

We found a higher prevalence of the SAS in patients aged between 50-59 years (39.6%) followed by those aged 60-69 years (24.75%) while the minimum prevalence was recorded in subjects over 80 years. SAS was more prevalent in T2DM patients (51.9%) in comparison with T1DM patients (31.8%).

Statistical analysis identified a significant difference between patients with or without SAS only for diabetes duration ($\chi^2_c = 4.35 > \chi^2_{1,0.05,1} = 3.84$) (Figure 2) and BMI ($\chi^2_c = 4.2 > \chi^2_{1,0.05,1} = 3.84$) (Figure 3).

Comparing the laboratory parameters of patients with and without SAS, we found that patients with SAS have a poorer metabolic control, lipid profile, urinary albumin excretion rates and liver enzyme tests, as shown in Table 1.

Thus, we could identify the profile of diabetic subjects of the patients with pulse-oximetry profile highly suggestive for the presence of SAS: obese T2DM males, aged 50-59 years, with a BMI of 30-35 kg/m², associated with dyslipidemia, increased urinary albumin excretion rates and liver enzymes, accompanied by chronic complications, especially neurologic/renal.

DISCUSSION

Despite the fact that the role of nocturnal ambulatory pulse-oximetry for the diagnosis and evaluation of SAS is not firmly established, it represents a useful tool for the diagnosis of sleep respiratory disturbances. It is a cheap and accessible method using a software that allows recording of the nocturnal oxygen saturation levels. It analyzes and synthesizes the characteristics of

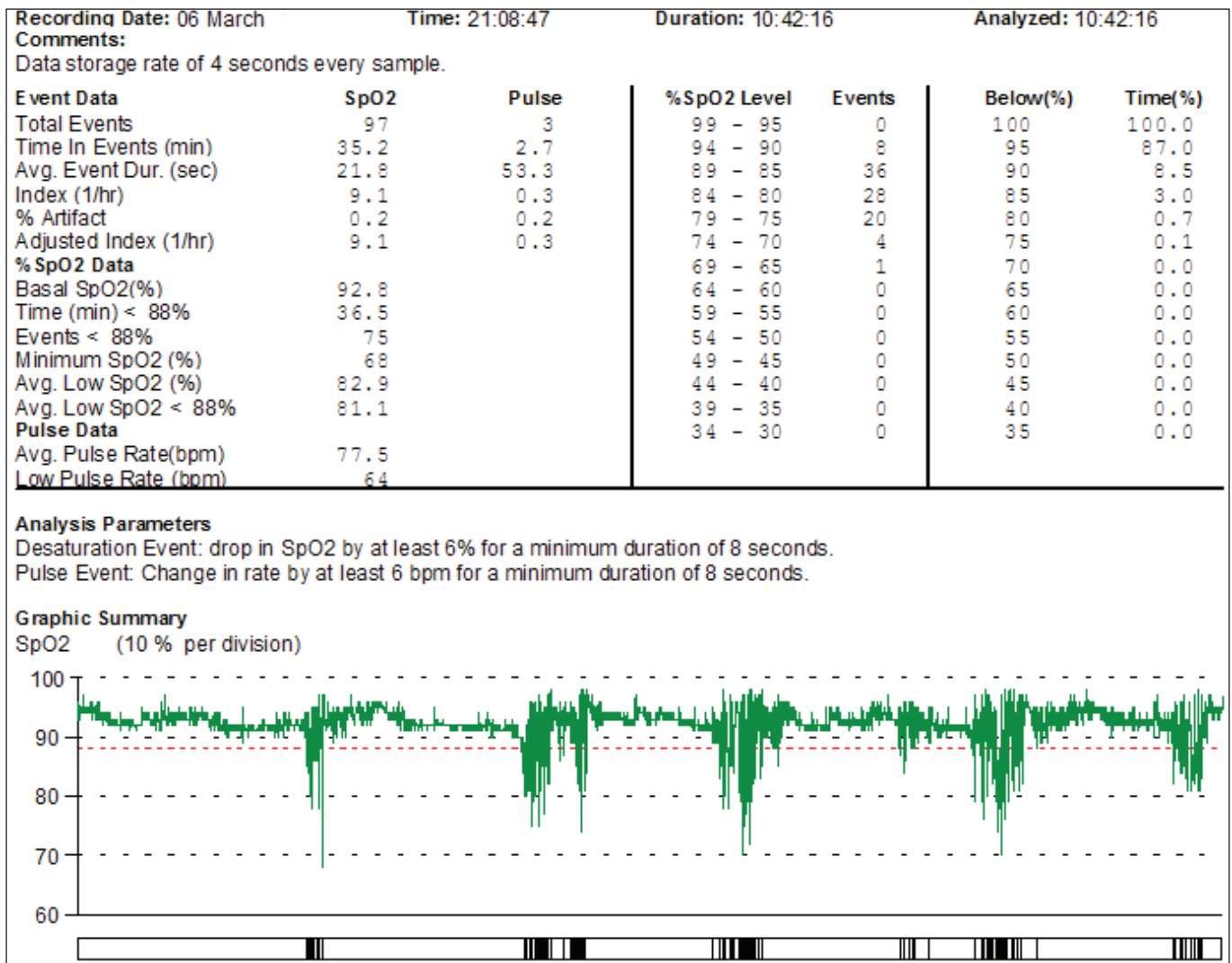


Figure 1. An example of an Oximetry Report in a SAS patient.

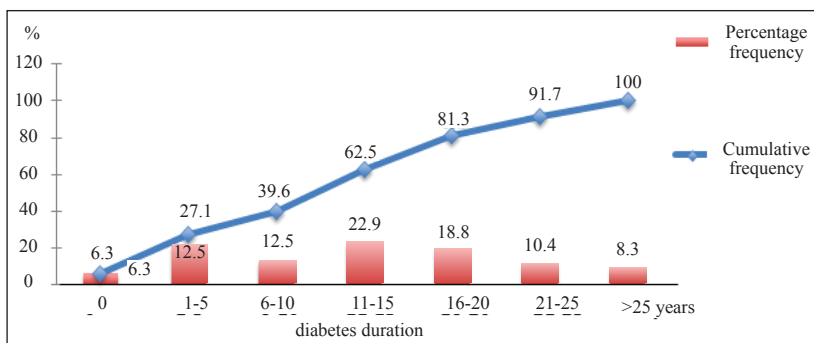


Figure 2. Percentage and cumulative prevalence of SAS according to diabetes duration.

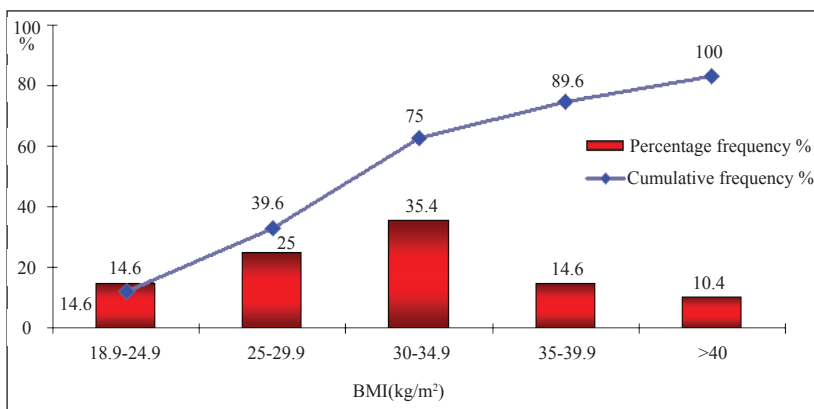


Figure 3. Percentage and cumulative SAS prevalence according to BMI

desaturation events allowing the identification of the sawtooth pattern characteristic for sleep apnea. Pulse-oximetry could be particularly helpful in identifying the patients with sleep respiratory disturbances and selection of those who necessitate polysomnography for diagnosis confirmation and especially for initiation of specific treatment. The interest for such a screening tool was evidenced by the last consensus statement of the American Thoracic Society [13]. According to these guidelines, only two isolated symptoms (hyper and hyposomnia) should lead systematically to polysomnography studies.

In the diabetes clinic, overlap between the symptoms of metabolically unstable diabetes and SAS (daytime sleepiness, fatigue, depression, polyuria, insomnia, altered sleep pattern, etc.) is frequent and distinguishing the two can be made only by a careful case history and clinical judgment. Continuous nocturnal oximetry can be sufficient for the diagnosis of SAS based on the magnitude and frequency of nocturnal desaturations interpreted in the context of suggestive clinical data.

Table 1. Metabolic profile of patients with SAS in comparison with those without SAS

Laboratory Parameters	SAS (-) % of total	SAS (+) % of total	Statistical significance of the observed differences	
HbA1c > 9 %	45%	54%	No	$c_c^2 = 1,04 < c_{t,0.05;1}^2 = 3,84$
Total cholesterol > 200 mg/dl	32%	52%	Yes	$c_c^2 = 5,47 > c_{t,0.05;1}^2 = 3,84$
HDL cholesterol < 35(M)/40(F) mg/dl	34 %	37 %	No	$c_c^2 = 1,4 < c_{t,0.05;1}^2 = 3,84$
Triglycerides > 150 mg/dl	34%	56%	Yes	$c_c^2 = 5,55 > c_{t,0.05;1}^2 = 3,84$
Urinary Albumin/Creatinine Ratio > 30mg/g	24%	46%	Yes	$c_c^2 = 4,35 > c_{t,0.05;1}^2 = 3,84$
Uric acid > 6 mg/dl (F) / 7 mg dl (M)	32%	54%	No	$c_c^2 = 1,09 < c_{t,0.05;1}^2 = 3,84$
TGP > 40 UI	15%	52%	Yes	$c_c^2 = 2,9 < c_{t,0.05;1}^2 = 3,84$

Sleep apnea leads to increased irritability and aggression, both associated with an increased risk for heteroaggressive events, including aggressive driving. For example, Booth *et al.*, by studying the overall aggressiveness of patients with sleep apnea before and after continuous positive airway pressure, revealed a significant decrease in aggression and hostility after treatment[14]. Vakulin *et al.* found SAS to lead to reduced driving simulator performance and increased risk for motor vehicle accidents, both augmented by alcohol consumption[15]. Diabetes is also known to be associated with impaired driving, the crash risk amongst diabetic patients being 1.19 (95% CI, 1.08-1.31) compared to non-diabetic patients [16]. As our study revealed an increased association between diabetes and SAS, the cumulative risk for motor vehicle accidents may be significantly increased.

CONCLUSION

In conclusion, our study found that up to 47% of patients admitted in a diabetes clinical ward exhibit oxygen saturation abnormality suggestive for the presence of SAS. We found a significant correlation between the severity of oxygen desaturation (total number of events and desaturation index) and the presence of the graphic pattern specific for SAS. Even if only marginally significant, we can state that subjects with SAS are more frequently overweight or obese and exhibit metabolic abnormalities of the metabolic syndrome. Nocturnal pulse-oximetry could be used as a surrogate method for the detection of SAS subjects. It allows reconsideration of the diagnostic priorities and referral of selected cases for more expensive polysomnography studies.

References

- Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009;5(3):263–276.
- Lecomte P, Criniere L, Fagot-Campagna A, Druet C, Fuhrman C. Underdiagnosis of obstructive sleep apnoea syndrome in patients with type 2 diabetes in France: ENTRED 2007. *Diabetes Metab.* 2012 Dec 3. doi:pii: S1262-3636(12)00200-5. 10.1016/j.diabet.2012.10.004. [Epub ahead of print].
- Redline S, Quan SF. Sleep apnea: a common mechanism for the deadly triad--cardiovascular disease, diabetes, and cancer? *Am J Respir Crit Care Med* 2012 Jul 15;186(2):123-124.
- Fusetti M, Fioretti AB, Valenti M, Masedu F, Lauriello M, Pagliarella M. Cardiovascular and metabolic comorbidities in patients with obstructive sleep apnoea syndrome. *Acta Otorhinolaryngol Ital* 2012;32(5):320-325.
- Tamura A, Kawano Y, Watanabe T, Kadota J. Obstructive sleep apnea increases hemoglobin A1c levels regardless of glucose tolerance status. *Sleep Med* 2012;13(8):1050-1055.
- Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S et al. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med* 2012;186(5):434-441.
- Mason RH, West SD, Kiire CA, Groves DC, Lipinski HJ, Jaycock A et al. High prevalence of sleep disordered breathing in patients with diabetic macular edema. *Retina* 2012;32(9):1791-1798.
- Gu CJ, Li M, Li QY, Li N, Shi GC, Wan HY. Obstructive sleep apnea is associated with impaired glucose metabolism in Han Chinese subjects. *Chin Med J (Engl)* 2013;126(1):5-10.
- Ioja S, Weir ID, Rennert NJ. Relationship between sleep disorders and the risk for developing type 2 diabetes mellitus. *Postgrad Med* 2012;124(4):119-129.
- Carr GE, Mokhlesi B, Gehlbach BK. Acute cardiopulmonary failure from sleep-disordered breathing. *Chest* 2012;141(3):798-808.
- Polysomnography Task Force, American Sleep Disorders Association Standards of Practice Committee. Practice parameters for the indications for polysomnography and related procedures. *Sleep* 1997;20(6):406–422.
- Poupard L, Philippe C, Goldman MD, Sartène R, Mathieu M. Novel mathematical processing method of nocturnal oximetry for screening patients with suspected sleep apnoea syndrome. *Sleep Breath* 2012;16(2):419-425.
- Kuna ST, Badr MS, Kimoff RJ, Kushida C, Lee-Chiong T, Levy Pet al. An official ATS/AASM/ACCP/ERS workshop report: Research priorities in ambulatory management of adults with obstructive sleep apnea. *Proc Am Thorac Soc* 2011;8(1):1-16.
- Booth BD, Paul Fedoroff J, Curry SD, Douglass AB. Sleep Apnea as a Possible Factor Contributing to Aggression in Sex Offenders*. *Journal of Forensic Sciences.* 2006;51(5):1178-1181.
- Vakulin A, Baulk SD, Catchside PG, Antic NA, Van Den Heuvel CJ, Dorrian J, et al. Effects of alcohol and sleep restriction on simulated driving performance in untreated patients with obstructive sleep apnea. *Annals of internal medicine.* 2009;151(7):447.
- Tregear SJ, Rizzo M, Tiller M, et al. Diabetes and motor vehicle crashes: a systematic evidence-based review and meta-analysis. In: *Proceedings of Driving Assessment 2007: The Fourth International Driving Symposium on Human Factors in Driver Assessment, Training, and Vehicle Design.* Iowa City: University of Iowa; 2007:343-350.