Applied Medical Informatics
Original Research Vol. 28, No. 2 /2011, pp: 41-46

Prevalence and Predictors of Excessive Daytime Sleepiness in Romanian Obese Type 2 Diabetic Patients

Adriana RUSU[1,2], Cristina NITA[1,2], Cornelia BALA[1,2], Nicolae HÂNCU[1,3]

[1] "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca, 13 Emil Isac, 400023 Cluj-Napoca, Romania.
[2] Clinical Center of Diabetes, Nutrition, Metabolic Diseases, Emergency County Hospital Cluj, 3-5 Clinicilor, 400006 Cluj-Napoca, Romania.
[3] Unirea Medical Center, 24 Louis Pasteur, 400349 Cluj-Napoca, Romania.
E-mails: adi.rusu@yahoo.com; cnita@umfcluj.ro; cbala@umfcluj.ro; nhancu@umfcluj.ro

* Author to whom correspondence should be addressed; Tel.: +4-0264-594455.

Received: 9 May 2011 /Accepted: 11 June 2011 / Published online: 15 June 2011

Abstract
Aim: The objective of this study was to determine the prevalence and to evaluate factors associated with excessive daytime sleepiness as a symptom of sleep apnea (SAS) in a sample of Romanian type 2 diabetic patients. *Material and Methods:* The Epworth Sleepiness Scale was administered to 242 consecutive patients with type 2 diabetes and a body mass index (BMI) ≥30kg/m². Score > 10 points was considered pathologic. *Results:* Twenty-two percent of diabetic obese patients had excessive daytime sleepiness. Compared with patients without daytime sleepiness, the median HbA1c was increased with 1.2% ($p<0.001$) in sleepy patients. Waist circumference (odds ratio: 1.04; 95%CI [1.01 – 1.07]), BMI (odds ratio: 1.1; 95%CI [1.04 – 1.18]) and HbA1c (odds ratio: 1.29; 95%CI [1.07 – 1.56]) were significantly related to the presence of excessive daytime sleepiness. *Conclusion:* Excessive daytime sleepiness as a symptom of suspected SAS is highly prevalent in Romanian patients with type 2 diabetes and should be systematically screened for, especially among obese individuals with higher waist circumference, higher BMI and higher HbA1c values.

Keywords*:* Daytime sleepiness; Obesity; Diabetes.

Introduction

Recently, there has been increasing recognition that sleep-disordered breathing is frequently associated with type 2 diabetes, and the observed association has important clinical and public health implications [1]. A possible explanation for this association is the presence of shared risk factors such as obesity, visceral adiposity and advancing age.

Sleep apnea syndrome represents an ensemble of signs and symptoms caused by repetitive episodes of absence (apnea) or reduction (hypopnea) of the airflow at the nose/mouth during the sleep, associated with fall in oxygen saturation, arousals and awakenings [2]. Sleep apnea is a general term encompassing two distinct entities, central sleep apnea and obstructive sleep apnea (OSA) [2]. OSA syndrome is characterized by the repetitive episodes of upper airway obstruction during sleep, that results in sleep fragmentation (frequent arousals to reestablish breath), recurrent hypoxemia, hypercapnia. These can lead to neurocognitive decline, cardiovascular complications, and eventually death [3]. Excessive daytime sleepiness is usually assumed to be one of the clinical symptoms of sleep disturbances (e.g. sleep apnea). Sleep deprivation, sedating medications, certain

medical and psychiatric conditions represents other causes of excessive daytime sleepiness [4]. Another cause of the daytime sleepiness in patients with diabetes are the increased levels of inflammatory cytokines [5]. In present, these cytokines are accepted as mediators of sleepiness [5], and they are closely involved in the pathogenesis of type 2 diabetes [6]. The Epworth Sleepiness Scale (ESS) represents a validated questionnaire containing eight items that measure a subject's expectation of dozing in eight hypothetical situations [7]. A score greater then 10 is considered indicative of excessive daytime sleepiness and there is a high suspicion of sleep disordered breathing [8].

The aim of this study was to determine the prevalence of excessive daytime sleepiness as a symptom of sleep apnea syndrome in a representative sample of Romanian patients with obesity and type 2 diabetes attending outpatient clinic of a diabetes center and to evaluate factors associated with the presence of excessive daytime sleepiness in this group of patients.

Material and Method

Between January 2008 and February 2010 every first 3 patients with type 2 diabetes and obesity presenting daily for routine visit in an outpatient clinic of Diabetes, Nutrition and Metabolic Diseases from Cluj-Napoca were invited to participate in the study. All study participants had type 2 diabetes (defined according to World Health Organization criteria [9]), a body mass index (BMI) $\geq 30 kg/m^2$ and were required to sign an informed consent before beginning the study procedures. Patients were not included in the study if they had type 1 diabetes, other specific diabetes forms, current diagnosis of SAS, or refused to sign an informed consent form. Basically, study protocol followed the protocol used in a previous pilot study [10].

The sample size was calculated with Cochran's formula [11]:

$$n \equiv [(t*2)\times p\times q]\div(d*2)$$

where: t = value for selected alpha level of 0.025 in each tail (the alpha level of 0.05) = 1.96; (p)(q) = estimate of the variance; d = acceptable margin of error for proportion being estimated = 0.05.

The variance was estimated based on a pilot study [12], which revealed a prevalence of symptomatic sleep apnea of 20%. We calculated that a sample size of 246 patients with type 2 diabetes and obesity will be needed to obtain a 95% confidence interval and ±5% precision, if the estimated prevalence of symptoms of sleep apnea will be at least 20%. After the correction for finite population, we obtained a sample size of 242 patients.

The Epworth Sleepiness Scale (a validated questionnaire containing eight items that measure a subject's expectation of dozing in eight hypothetical situations [13]) was administered to study participants. A score of > 10 was considered indicative of excessive daytime sleepiness and there was a high suspicion of sleep disordered breathing.

A complete medical history, including diabetes duration, diabetes treatment, diabetic complications and physical examination were performed. Height, weight, waist circumference, hip circumference and blood pressure were determined by a standardized protocol. Waist circumference was measured half way between the lower border of the last rib and the upper border of the iliac crest at the end of a normal expiration, using a non-stretchable tape measure. Hip circumference was measured around the maximum circumference of the buttocks. Body mass index (BMI) was calculated as weight (kg)/ [height (m)] ^{2}. BP was measured using a standard mercury sphygmomanometer. All readings were taken after a 5-minute rest, with the patient in the sitting position.

Fasting blood samples were drawn from every individual, in order to assess the levels of glycemia, glycosilated hemoglobin (HbA1c), total cholesterol, HDL-cholesterol and triglycerides. LDL-cholesterol was calculated using Friedewald formula [14].

Statistical Analysis

Statistical analysis was carried out using SPSS-PC 15.0 (SPSS Inc., Chicago, IL, USA). Skewness and kurtosis, as well as Kolmogorov-Smirnov test were used to test the normal distribution of the

variables. Data are reported as means and standard deviation for variables with normal distribution and as median and 1st and 3rd quartile for variables with an abnormal distribution. For comparative analysis were applied: t-test (for continuous variables with normal distribution), chi square test for dichotomial variables, Mann-Whitney U-test (for variables with a distribution that differs from a normal one). The associations between excessive daytime sleepiness and other variables were assessed by Spearman correlation coefficients and logistic regression (in order to determine Odds Ratio (OR)). The level of significance was set at 0.05, and all tests were performed two sided.

Results

Present analysis included 125 women and 117 men, minimum age 31 years, maximum age 79 years with a mean BMI of 36 kg/m^2 (range from 30.0 kg/m^2 to 51.5 kg/m^2) (Table1). Stratification for antidiabetic treatment was as follows: 6.3% were on diet alone, 51.2% on oral therapy and 42.5% on insulin (alone or in combination with oral therapy).

Table 1. Characteristics of study participants

Parameter	Value
Age (years) = mean±SD	58.5 ± 9.1
Men (%)	48.3
Duration of diabetes (years) mean±SD	7.1±5.6
Waist circumference (cm) mean±SD	118.4 ± 11.8
BMI (kg/m^2) - body mass index mean±SD	35.9 ± 4.7
Waist to hip ratio*	1.0 (0.9;1.1)
Fasting blood glucose (mg/dl) mean±SD	151.9±48.5
HbA1c (%)* - glycosilated hemoglobin	7.4 (6.6;8.6)

*-Variables with abnormal distribution are presented as median (1st quartile; 3rd quartile)

Based on results obtained at the Epworth Sleepiness Scale, 22.7% of the study participants (55 patients) presented excessive daytime sleepiness. Of these, 22 were females (17.6%) and 33 were men (28.2%) (Chi square test Statistics; p=0.04).

Characteristics of patients with or without excessive daytime sleepiness are presented in Table 2. Compared to patients without excessive daytime sleepiness, median HbA1c was increased with 1.2% (Mann-Whitney U-test; p<0.001) in sleepy patients. The prevalence of diabetic peripheral neuropathy and diabetic nephropathy was significant higher in patients with excessive daytime sleepiness. The prevalence of diabetic retinopathy was higher in group with excessive daytime sleepiness compared with patients without excessive daytime sleepiness, but the difference did not achieved the level of statistical significance. The other characteristics included in analysis were not statistically significant different between the two groups.

Spearman's correlation coefficients were calculated to assess the association between the presence of excessive daytime sleepiness and other variables. Only sex, age, BMI, waist and HbA1c were significantly correlated with the presence of excessive daytime sleepiness.

These variables were further included in a univariate logistic regressions analysis in order to identify predictors of excessive daytime sleepiness (Table 3). Only age, waist, BMI and HbA1c were significantly associated with the presence of excessive daytime sleepiness after regression analysis. In other words, excessive daytime sleepiness odds increased with 4% with every 1 cm increase in abdominal circumference (95%CI: 1.01 – 1.07) and with 10% with every 1 kg/m^2 increase in BMI (95%CI: 1.04 – 1.18). Also, excessive daytime sleepiness odds increased with 29% with every 1% increase in HbA1c (95%CI: 1.07 – 1.56).

Table 2. Characteristics of patients with/without excessive daytime sleepiness

Characteristics	Excessive daytime sleepiness (n=55)	Non excessive daytime sleepiness (n=187)	p
Male/female gender	33/22	84/103	0.04
Age (years)	59.7±9.2	54.6±7.9	< 0.001
BMI ((kg/m²)	37.7±5.4	35.4±4.3	0.005
Waist circumference (cm)	123.1±12.4	117.0±11.3	0.001
Systolic BP (mmHg)	147.5±23.4	148.9±20.4	0.68
Diastolic BP (mmHg)	86.0±14.0	88.5±12.7	0.22
Total cholesterol (mg/dl)	182.9±85.2	181.7±42.1	0.89
HDL-cholesterol (mg/dl)	40.4±9.0	44.6±10.6	0.007
LDL-cholesterol (mg/dl)	94.1±31.1	102.1±36.3	0.16
Triglycerides (mg/dl) *	181.5.0(107.0;255.0)	151.5(112.1;219.0)	0.36
FPG (mg/dl)	167.3±64.3	147.6±42.4	0.04
HbA1c (%)*	8.5 (7.2;9.8)	7.3 (6.4;8.4)	<0.001
Duration of diabetes (years)	7.5±5.9	7.0±5.5	0.57
Diabetic retinopathy (%)	26.4	18.5	0.14
Diabetic neuropathy (%)	41.5	28.8	0.04
Diabetic nephropathy (%)	16.7	7.1	0.03

BMI = body mass index; BP = blood pressure; FPG = fasting plasma glucose; HbA1c = glycosilated hemoglobin; CVD = cardiovascular disease.
Data in Table are presented as mean±SD for continuous variables or % for dichotomial variables; *-Variables with abnormal distribution are presented as median (1st quartile; 3rd quartile)

Table 3. Unadjusted odds ratio (95% CI) for the presence of excessive daytime sleepiness and different variables estimated by unadjusted logistic regression

Characteristics	Excessive daytime sleepiness (all patients)
Age	1.06 (1.03 – 1.10)
Male sex	1.80 (0.99 – 3.39)
BMI	1.10 (1.04 – 1.18)
Waist	1.04 (1.01 – 1.07)
HbA1c	1.29 (1.07 – 1.56)

CI = confidence interval;
BMI = body mass index; HbA1c = glycosilated hemoglobin

Discussions

The main finding of this study was the high prevalence of excessive daytime sleepiness in patients with type 2 diabetes (22.3%). Individuals with excessive daytime sleepiness were more frequently males, older, had higher BMI, waist circumference and lower HDL-cholesterol compared with non-sleepy subjects. Other findings were that age, waist circumference, BMI and HbA1c were independent predictors of the presence of excessive daytime sleepiness.

Compared with studies conducted on diabetic patients, this study revealed lower prevalence of excessive daytime sleepiness.

In a similar study Kelly et al [15], examined the risk of having sleep apnea by Epworth Sleepiness Scale in a population of obese patients with type 2 diabetes from a district general hospital diabetes clinic. This article reported a prevalence of ESS >10 of 56%, higher then in the present report. This difference could be explained by the number of patients included in these researches: 66 in the study conducted by Kelly and 242 patients in the present report. Also, the selection of these patients was different (patients in our study were selected from an outpatient

clinic which is the standard for routine care in Romania; patients included in article published by Kelly et al patients were selected from those admitted in a diabetes unit from a general hospital). We tried to avoid a selection bias by inviting to participate every day the first 3 patients with type 2 diabetes and obesity who presented for a routine visit.

In our study, excessive daytime sleepiness was more common in men, and was associated with a higher BMI, waist circumference and advanced age. These results are similar with those of Einhorn and colleagues [16] and Kelly et al [15]. In a study conducted on 330 patient with type 2 diabetes, Einhorn et al demonstrated that subjects with sleep apnea were more likely to be males, had a higher BMI and were older (>62 years of age) than the subjects without sleep apnea [16]. In our study, both BMI and waist circumference were predictors of the presence of excessive daytime sleepiness, even after adjustment for age and male sex.

Even more concerning is the fact that in patients with excessive daytime sleepiness the median HbA1c was increased with 1.2% ($p<0.001$) compared with patients without excessive daytime sleepiness. These results are comparable with those observed by Aronshon and collab [17]. They demonstrated that „increasing severity of OSA is associated with poorer glucose control, with effect size comparable to those of several hypoglycemic drugs". Our study demonstrated an association between the presence of excessive daytime sleepiness and the HbA1c value: excessive daytime sleepiness odds increased with 29% with every 1% increase in HbA1c (95%CI: 1.07 – 1.56).

There are some limitations of our study: 1) the cross-sectional design that does not allow us to make any conclusive statement about the temporality of the observed associations, and 2) selecting a sample from an outpatient clinic could lead to a selection bias (even if the specialist consultation is the standard for primary care of patients with diabetes in Romania).

Conclusion

Excessive daytime sleepiness is highly prevalent in Romanian patients with type 2 diabetes and should be systematically screened for, especially among obese individuals with higher waist circumference and poor diabetes control.

Ethical Issues

The research was conducted in accordance with the guidelines in The Declaration of Helsinki and the medical ethical committee of the "Iuliu Haţieganu" University of Medicine and Pharmacy Cluj-Napoca approved the study protocol.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Shaw JE, Punjabi NM, Wilding JP, Alberti KG, Zimmet PZ; International Diabetes Federation Taskforce on Epidemiology and Prevention. Sleep-disordered breathing and type 2 diabetes: a report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract 2008;81:2-12.
2. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667-89.

3. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A et al. Sleep Apnea and Cardiovascular Disease: An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing In Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health). Circulation 2008;118:1080-111.
4. Pagel JF. Excessive Daytime Sleepiness. Am Fam Physician 2009;79:391-6.
5. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J Clin Endocrinol Metab 1997;82:1313-6.
6. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813-23.
7. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea- the Epworth Sleepiness Scale. Chest 1993;103:30-6.
8. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540-5.
9. Organization World Health. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycemia: Report of a WHO/IDF Consultation. . Geneva,Switzerland: WHO; 2006.
10. Rusu A, Todea D, Rosca L, Nita C, Bala C. The development of a sleep apnea screening program in Romanian type 2 diabetic patients: a pilot study. Acta Diabetol 2010;DOI: 10.1007/s00592-010-0177-5.
11. Cochran W. Sampling Techniques. New York: John Wiley & Sons; 1977.
12. Rusu A, Todea D, Rosca L, Nita C, Bala C. The development of a sleep apnea screening program in Romanian type 2 diabetic patients: a pilot study. Acta Diabetol 2010;DOI:10.1007/s00592-010-0177-5.
13. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea- the Epworth Sleepiness Scale. Chest 1993;103:30-6.
14. Friedewald WT, Levy RI, Friedrickson DS. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clin Chem 1972;18:499- 502.
15. 15. Kelly E, Cullen G, McGurk C. Obstructive sleep apnoea in patients with type 2 diabetes. Thorax 2007;62:651.
16. Einhorn D, Stewart DA, Erman MK, Gordon N, Philis-Tsimikas A, Casal E. Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. Endocr Pract 2007;13:355-62.
17. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of Untreated Obstructive Sleep Apnea on Glucose Control in Type 2 Diabetes. Am J Respir Crit Care Med 2010;181:507-13.