Excessive daytime sleepiness in type 2 diabetes

Sonolência excessiva diurna em diabetes tipo 2

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ABSTRACT

Objective: To examine excessive daytime sleepiness (EDS) in type 2 diabetes. **Subjects and methods:** Patients (N = 110) were evaluated regarding Epworth Sleepiness Scale (EDS), sleep quality (Pittsburgh Sleep Quality Index), depressive symptoms (Beck Depression Inventory), Restless Legs Syndrome (RLS), risk of obstructive sleep apnea (OSA) (Berlin questionnaire), and comorbidity severity (Charlson Comorbidity Index). Patients were compared with individuals with arterial hypertension and without diabetes. **Results:** Diabetic patients had more EDS, depressive symptoms, and higher comorbidity severity than hypertensive patients ($p < 0.005$). In diabetic patients, poor quality sleep (53.3%), and high risk of OSA (40.9%) and RLS (14.5%) were found; EDS (55.5%) was associated with depressive symptoms present in 44.5% individuals (OR = 1.08; 95% CI: 1.01-1.15), and remained so after data were controlled for age, gender, body mass index, and glycated hemoglobin (OR = 2.27; 95% CI 1.03-5.03). **Conclusions:** Sleep abnormalities are frequent. EDS affects most of the patients and is independently associated with depressive symptoms. Adequate antidepressant therapy should be tested for the effects on EDS. Arq Bras Endocrinol Metab. 2013;57(6):425-30

Keywords

Diabetes; sleep; depression; apnea; comorbidity

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RESUMO

Objetivo: Em pacientes com diabetes tipo 2, avaliar a sonolência excessiva diurna (SED). **Sujeitos e métodos:** Pacientes (N = 110) foram investigados com relação a Escala de Sonolência de Epworth (SED), qualidade do sono (Índice de Qualidade de Sono Pittsburgh), sintomas depressivos (Inventário de Depressão de Beck), Síndrome das Pernas Inquietas (SPI), risco de apneia obstrutiva do sono (AOS) (Questionário de Berlim) e comorbidades (Índice de Comorbidade de Charlson), e foram comparados com indivíduos com hipertensão arterial sem diabetes. **Resultados:** Pacientes diabéticos apresentavam mais SED, sintomas depressivos e comorbidades que os hipertensos ($p < 0,005$). Em pacientes diabéticos, má qualidade do sono (53,3%), risco de AOS (40,9%) e SPI (14,5%) foram encontrados. SED (55,5%) associou-se com os sintomas depressivos em 44,5% (OR = 1,08; 95% IC 1,01-1,15) e permaneceu após controle para idade, sexo, índice de massa corporal e hemoglobina glicosilada (OR = 2,27 95% IC 1,03-5,03). **Conclusões:** Anormalidades do sono são frequentes. SED afeta a maioria dos pacientes e associa-se de forma independente com os sintomas depressivos. Terapia antidepressiva pode melhorar a SED. Arq Bras Endocrinol Metab. 2013;57(6):425-30

Descritores

Diabetes; sono; depressão; apneia; comorbidade

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INTRODUCTION

Daytime somnolence and inattention are potential causes for accidents, cognitive decline, and reduced work efficiency (1). Previous studies have linked sleepiness with higher morbidity and mortality rates in various clinical settings (2,3). Increasing attention has been paid to the connection between diabetes and excessive daytime sleepiness (4,5). It has been suggested that diabetic patients are more likely to be sleepy during the daytime than non-diabetic ones (6,7); moreover, greater risk for traffic accidents due to somnolence has been shown in diabetic patients (8). It has also been found that sleepiness is associated with a general decrease in motivation to engage in activities that are important in the management of diabetes (5).

Despite the recognition of sleepiness as a major public health issue (9), its clinically associated factors and pathogenesis have not been totally clarified. Previous studies indicate that, among the general population, excessive daytime sleepiness has been more strongly associated with depression and obesity than with metabolic factors, sleep-disordered breathing, or sleep disruption (10,11). Interestingly, in elderly people, sleep alterations have been associated with depression, cognitive decline, and diabetes (12). It has also been pointed out that increased daytime sleepiness does not seem to be driven only by the presence of obstructive sleep apnea (OSA). In fact, a study has suggested that several clinical factors such as obesity, metabolic abnormalities, or inflammatory markers may play a role in the genesis of excessive daytime sleepiness (13). Therefore, increased daytime sleepiness in type 2 diabetes may be associated with sleep disorders such as OSA (14), insomnia (15), and restless legs syndrome (16). After considering all the above, understanding the associations between sleep disorders and daytime somnolence in type 2 diabetes may contribute to therapy in these patients.

The aim of this study was to evaluate excessive daytime sleepiness in type 2 diabetes and its associations with depressive symptoms, other sleep complaints, and clinical/laboratory variables.

MATERIALS AND METHODS

Study design and participants

This is a cross-sectional study of individuals with type 2 diabetes. We evaluated 113 consecutive men and women with type 2 diabetes who presented for clinical follow-up in an outpatient diabetes clinic. Three subjects refused to answer the questionnaires and were withdrawn from the sample. Inclusion criteria were the diagnosis of type 2 diabetes, clinical stability, and no change of medication in the previous three months. Exclusion criteria were working in the night shift, history of alcohol or drug abuse, presence of cancer or of severe neurologic, renal, or cardiac diseases. Data from diabetic patients were compared with a group of patients with arterial hypertension and without diabetes (n = 36). The protocol was approved by the local Research Ethics Committee, and written informed consent was obtained for all subjects (CEP/HUWC 031.04.09).

Outcome measures

Demographic data, habits, and comorbidities were recorded using a standardized questionnaire. Biochemical data were collected from patient files. Body mass index (BMI) was calculated as the ratio between weight (kg) and squared height (m^2). Daytime somnolence was assessed by the Epworth Sleepiness Scale (ESS), a questionnaire containing eight items that ask about the expectation of dozing in eight hypothetical situations. Epworth Sleepiness Scale score greater than 10 indicates excessive daytime sleepiness (17). Subjective sleep quality was evaluated by the Pittsburgh Sleep Quality Index (PSQI). Pittsburgh Sleep Quality Index has seven components, each one dealing with a major aspect of sleep: subjective quality of sleep, sleep onset latency, sleep duration, sleep efficiency, and presence of sleep disturbances. Individuals with total PSQI score greater than six were considered poor sleepers (18). Depressive symptoms were evaluated by the Beck Depression Inventory (BDI), and were defined as present if the score was greater than 10 (19). Frequent associated comorbidities, such as hypertension, high risk of OSA, and restless legs syndrome, which might influence excessive daytime sleepiness, were analyzed. Restless leg syndrome was identified using the minimum criteria defined by the International Restless Legs Syndrome Study Group: 1) an urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs; 2) the urge to move or the beginning or worsening of unpleasant sensations happening during periods of rest or inactivity, such as lying or sitting; 3) the urge to move or unpleasant sensations being partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; and 4) the urge to move or unpleasant sensations being

worse in the evening or night than during the day, or occuring only in the evening or night (20). This scale has been adapted to Brazilian patients (21). Risk of having OSA were assessed by the Berlin questionnaire (22). In order to assess the influence and presence of associated comorbidities, the Charlson Comorbidity Index (CCI) was used (23).

Statistical analysis

Data are expressed as mean ± SD values. Comparisons between diabetic patients and subjects with arterial hypertension and without diabetes were performed. Diabetic patients were grouped as having excessive daytime sleepiness or not. Fisher exact tests for categorical variables, Mann-Whitney *U* test for continuous variables, and Student's t test for normally distributed data with equal variances were performed to compare cases and controls. Logistic regression analysis was used to examine associations between clinical and demographic variables, and excessive daytime sleepiness. Posterior adjustments for age, gender, BMI and glycated hemoglobin were performed. Statistical analysis was performed with the Statistic Package for Social Sciences (SPSS – Norusis, 1993) software for Windows. The level of significance was set at $p < 0.05$.

RESULTS

A total of 110 type 2 diabetes patients, 73 (65.8%) females with a mean age of 57.6 ± 11.0 years and 36 individuals with arterial hypertension, 21 (58.3%) female, mean age 57.6 ± 9.7 were studied. Patients with diabetes showed greater comorbidity severity as evaluated by the CCI, more depressive symptoms as evaluated by the BDI, and more severe excessive daytime sleepiness ($p < 0.005$). Subjects with arterial hypertension had worse sleep quality as evaluated by the PSQI ($p < 0.005$) (Table 1). In diabetic patients, excessive daytime sleepiness was present in 55.5% of cases. This was not related to gender, age, disease duration, BMI, waist-hip ratio, and laboratory results (Table 2). Diabetic patients with excessive daytime sleepiness showed significantly higher BDI scores than non-diabetic patients (11.43 ± 6.79 *vs.* 8.43 ± 6.0, $p = 0.01$, respectively). An association between excessive daytime sleepiness and depressive symptoms was found (OR = 1.08; 95% CI: 1.01-1.15), and remained significant after data were controlled for age, gender, BMI, and glycated hemoglobin (OR = 2.27; 95% CI: 1.03-5.03) (Table 3). In diabetic patients, poor sleep quality was found in 53.3% of the cases, and was not associated with daytime sleepiness. Restless leg syndrome was found in 14.5% of the cases and arterial hypertension in 70.0%; neither was associated with excessive daytime sleepiness. The risk of OSA, as defined by the Berlin questionnaire, was present in 40.9% of the patients, and was not associated with excessive daytime sleepiness. Comorbidity severity as evaluated by the CCI was not associated with excessive daytime sleepiness. The most common complications associated with diabetes were peripheral neuropathy (31.2%), retinopathy (17.8%), cataract (19.0%), and renal disease (5.4%). Depressive symptoms were present in 44.5% of diabetic patients and were associated with poor sleep quality as evaluated by the PSQI (OR = 1.39; 95% CI: 1.21-1.59).

Table 1. Demographic characteristics and clinical factors of subjects with diabetes and hypertension

	Diabetes	Hypertension	*p* value
Gender M/F	38/72	15/21	[a] 0.43
Age (years)	57.59 ± 11.04	57.58 ± 9.70	[b] 0.99
BMI	27.55 ± 4.79	29.41 ± 5.85	[b] 0.06
ESS	10.72 ± 5.81	6.00 ± 3.84	[c] 0.000**
BDI	10.09 ± 6.59	5.94 ± 3.95	[c] 0.000**
PSQI	7.40 ± 4.22	15.00 ± 7.82	[c] 0.000**
CCI	2.24 ± 1.59	0.47 ± 0.84	[c] 0.000**
Risk of OSA (Yes/No)	45/65	17/19	[a] 0.21

ESS: Epworth Sleepiness Scale; M/F: Male/Female; BMI: Body Mass Index; BDI: Beck Depression Inventory; PSQI: Pittsburgh Sleep Quality Index; CCI: Charlson Comorbidity Index; OSA: Obstructive Sleep Apnea.
[a] Fisher Exact Test; [b] Student's Test; [c] Mann-Whitney Test.

Table 2. Clinical, laboratory, and demographic characteristics of subjects with and without excessive daytime sleepiness

	ESS ≤ 10 n = 49	ESS > 10 n = 61	Unadjusted p value
Gender M/F	16/33	22/39	[a] 0.84
Age (years)	55.8 ± 11.7	58.89 ± 10.38	[b] 0.14
BMI	27.84 ± 5.62	27.28 ± 4.00	[b] 0.55
Waist-hip ratio (cm)	0.93 ± 0.09	0.93 ± 0.06	[b] 0.79
Disease duration (years)	10.10 ± 7.94	10.53 ± 7.29	[b] 0.80
Hemoglobin (g/dL)	12.79 ± 3.06	13.03 ± 1.79	[b] 0.74
Glycated hemoglobin (%)	8.83 (2.77)	8.71 (2.63)	[b] 0.85
Cholesterol (mg/dL)	200.5 ± 42.1	204.5 ± 43.2	[b] 0.72
Triglycerides (mg/dL)	526.5 ± 172.3	315.0 ± 118.3	[b] 0.43
HDL (mg/dL)	39.3 ± 12.3	43.3 ± 10.1	[b] 0.12

ESS: Epworth Sleepiness Scale; M/F: Male/Female; BMI: Body Mass Index; cm: centimeter; HDL: High Density Lipoprotein.
[a] Fisher Exact Test; [b] Student's Test; [c] Mann-Whitney Test.

Table 3. Clinical factors associated with excessive daytime sleepiness based on multiple logistic regression analysis

Model 1	Excessive daytime sleepiness	
	OR (95%CI)	*p* Value
Beck Depression Inventory	1.08 (1.01-1.15)	0.02*
Pittsburgh Sleep Quality Index	1.08 (0.98-1.19)	0.09
Charlson Comorbidity Index	1.19 (0.91-1.55)	0.18
Restless Legs Syndrome	1.32 (0.45-3.83)	0.60
Hypertension	1.38 (0.60-3.18)	0.44
High risk of obstructive sleep apnea (Berlin questionnaire)	0.33 (0.01-6.65)	0.47
Model 2		
Beck Depression Inventory	2.27 (1.03-5.03)	0.04*
Pittsburgh Sleep Quality Index	1.10 (0.96-1.25)	0.15
Charlson Comorbidity Index	1.21 (0.79-1.84)	0.36
Restless Legs Syndrome	0.81 (0.20-3.21)	0.77
Hypertension	0.54 (0.15-1.96)	0.35
High risk of obstructive sleep apnea (Berlin questionnaire)	1.02 (0.97-1.06)	0.42

Model 1: In this unadjusted model, Beck Depression Inventory scores, Pittsburgh Sleep Quality Index scores, and Charlson Comorbidity Index scores were entered as numerical variables, and Restless Legs Syndrome, Hypertension, and High risk of obstructive sleep apnea as dichotomized variables (present/absent). Hosmer-Lemeshow goodness-of-fit tests showed 9.65 and p _0.29 demonstrating a good fit of the models. **Model 2:** In this model, data was adjusted for age, gender, body mass index, and glycated hemoglobin.

DISCUSSION

These results show that excessive daytime sleepiness is common in type-2 diabetes and affects more than half of the patients. Of crucial importance is the fact that excessive daytime sleepiness was independently associated with depressive symptoms. This is in agreement with previous reports showing that daytime somnolence is linked with depressive symptoms in the general population (10) and in the elderly (12). Differently from the study of Bixler and cols., metabolic abnormalities were not found to influence excessive daytime sleepiness in diabetic patients (10). By comparison, diabetic patients showed more sleepiness, more depressive symptoms, and higher comorbidity severity than patients with hypertension. Interestingly, hypertensive patients without diabetes had worse quality of sleep. These findings may be related to the association between obstructive sleep apnea and hypertension (24). With regards to the presence of daytime sleepiness, differences in BMI were not found. This is in contrast to a previous report showing that obesity is associated with objective and subjective daytime sleepiness regardless of the presence of sleep apnea (10). In this report, the risk for sleep apnea was the same for diabetic patients with and without excessive daytime sleepiness. Also, despite prior reports showing gender differences in excessive daytime sleepiness (25) and depressive symptoms (26), no gender differences were found in this study. Together, these findings suggest that depressive symptoms play an important role in the genesis of daytime somnolence in type 2 diabetes. We cannot exclude other so far non-established abnormalities, such as the presence of inflammation, in the pathogenesis of daytime sleepiness. It has been previously suggested that a bidirectional relationship between depression and inflammation exists. Depression can result in an up--regulation of inflammatory mediators that can further contribute to daytime sleepiness (27). Furthermore, it has been demonstrated that increases in sleep duration are associated with elevations in C-reactive protein and interleukin-6 (28). This is a subject that needs further clarification. Prospective studies could test the effects of antidepressants in daytime somnolence, cognitive function, reduced alertness, and driving ability (29).

We confirm that poor sleep quality affects more than half of diabetic patients (16). An association between depressive symptoms and poor quality of sleep was found. In another group of patients and, in agreement with our findings, it has been shown that among the obese, the level of emotional stress is the key distinguishing factor between good sleepers and poor sleepers (30). Of interest, depression and diabetes were the most important determinants of daytime sleepiness in a population with OSA (31). The connection between reduced sleep, sleep apnea, and the posterior risk of developing diabetes has been suggested before (32). Considering the endemic situation of chronic sleep loss in modern society, it should be noticed that this public health issue may be contributing to increase the prevalence of diabetes worldwide. All this indicates that a therapeutic approach of depressive symptoms may not only increase the level of daytime alertness and daily activities but also improve sleep disturbances and glycemic control. A recent placebo-controlled, single-blind study evaluating the effects of exenatide, a medication for the treatment of type 2 diabetes, has shown significant reduction in objective sleepiness in obese patients with type 2 diabetes without OSA. The same study showed no significant change in depression and driving performance (33).

In this study, we confirm that restless leg syndrome is frequent in type 2 diabetes (16). Restless leg syndrome was present in 14.5% of cases, which is twice the expected values for a large population-based study (34).

Limitations of this study must be acknowledged. It was a cross-sectional evaluation, and a prospective study could clarify the effects of antidepressant on sleepiness in these patients. Also, sleepiness was a subjective measure, and objective measures of daytime sleepiness were not tested. The Multiple Sleep Latency test has been considered the gold standard objective method for sleepiness assessment (35). However, the ESS is used worldwide as a standard measure in the evaluation of excessive daytime sleepiness. Furthermore, it has been suggested that subjective measures and objective measures may assess different aspects of excessive daytime sleepiness (36): subjective sleepiness as evaluated by the ESS would mean a sleep dimension different from measures of objective sleepiness. Despite this controversy, ESS remains the most frequent used scale for the assessment of daytime sleepiness and therapeutic efficiency. It is worth noticing that the present data highlight the magnitude of daytime sleepiness and its association with depressive symptoms: these findings indicate the need to verify the potential modifying effects of antidepressants.

In summary, in diabetic patients, daytime somnolence is frequent and independently associated with depressive symptoms. We suggest that diabetic patients with excessive daytime sleepiness should be more thoroughly investigated for these symptoms. Proper therapy might improve alertness and psychological well-being leading to better cooperation and disease control.

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