Research Paper

May diabetes patients have trouble sleeping despite not having obesity?

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A B S T R A C T
Obstructive sleep apnea (OSA) and periodic limb movements during sleep (PLMs) are sleep-related disorders with a high prevalence in type 2 diabetes. Commonly OSA is considered as a consequence of obesity, but several previous studies have shown the presence of OSA in non-obese diabetic patients. A previous study showed higher PLMs prevalence in patients with type 2 diabetes, compared to age-matched controls. We speculated that both OSA and PLMs may reflect the presence of diabetic autonomic neuropathy. To test this hypothesis, we compared a group of 112 non-obese patients with type 2 diabetes with 66 age-, sex-, and body mass index- matched nondiabetic patients. Both groups have been investigated through a set of tests including the Epworth Sleepiness Scale, polysomnography, and the Orthostatic Grading Scale (OGS), a questionnaire to assess the degree of autonomic dysfunction. Diabetic patients with OSA and PLMs scored higher on the OGS than controls. Our results confirm that both OSA and PLMs are related to dysautonomy and may be unrelated to obesity in type 2 diabetes patients.

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Introduction

Sleep duration and quality modulates metabolic, endocrine, and cardiovascular functions [37]. Alterations in the control of blood sugar may gradually lead to serious dysregulation of sleep control and vice-versa.

A dramatic increase in the incidence of diabetes and obesity appears to develop simultaneously with decreased self-reported sleep duration; this may indicate a close relationship between diabetes and sleep disorder [36,39]. The Sleep Heart Health Study showed that diabetes patients had less time spent on REM sleep and more breathing episodes vs. people without diabetes [30]. In Type 2 diabetes, sleep disturbances are held to be common; they have been attributed to impaired glucose metabolism and general physical distress [16].

Obesity may constitute a risk factor for obstructive sleep apnea (OSA) [24], which is in turn associated with greater insulin resistance [13,29]. Both longer and shorter sleep duration increase the odds of having a metabolic syndrome [25], and poor sleep quality, as assessed with the Pittsburgh Sleep Quality Index, was found to negatively affect cardiovascular risk markers, like systolic blood pressure and blood lipid concentrations in type 2 diabetes patients [41]; in particular, severe OSA was found to be associated with greater cardiovascular risk and mortality, while OSA was positively associated with diabetes [10]. However, OSA and type 2 diabetes are associated with each other bidirectionally, and the presence of one may increase the risk of the other [1]. Diabetic autonomic neuropathy may be associated with increased OSA [7,44]. West et al. [44] showed a high prevalence of OSA in men with type 2 diabetes, concluding that diabetes itself may be a significant, independent contributor to the risk of OSA.

Recently Rizzi et al. [31] detected a greater prevalence of periodic limb movements during sleep (PLMS) in type 2 diabetes patients, compared age-matched healthy volunteers, probably due to an involvement of the sympathetic nervous system.
We aimed to investigate the presence of sleep disturbance in a cohort of diabetes type 2 non-obese patients and compare it with age- and sex-matched patients with other disorders seeking help at two different hospital services. We hypothesized that diabetes type 2 patients would present more sleep alterations than nondiabetic patients.

**Methods**

**Patients**

A group of 112 non-obese consecutive patients with type 2 diabetes were compared with a control group of 66 patients with other disorders who volunteered participating in the study and were age-, sex- and body mass index (BMI)-matched with the patients with diabetes. Patients and controls were consecutively recruited during the period January 2011–May 2012 from either the emergency department of the C. Cantù Hospital, Abbiategrasso, Milan, Italy (N = 71, 39 women, mean age, 56; standard deviation [SD], 21), or the pulmonary disorders unit of the Luigi Sacco Hospital, Milan (N = 41, 19 women, mean age, 51; SD, 18). All patients with diabetes were treated with metformin in the range of 500–1500 mg/day. Patients were included no matter whether they reported sleep problems or not.

Exclusion criteria comprised history of neurological or psychiatric disorders, alcohol or drug abuse, chronic renal failure or uremia, large fiber polyneuropathy (as assessed through standard nerve conduction studies), rheumatoid arthritis, anemia, hypothyroidism, chronic obstructive pulmonary disease, heart disease, liver cirrhosis, and B12 deficiency. This aimed to exclude that these conditions could affect peripheral nerve transmission, and obesity (BMI ≥ 30), that could affect sleep and be a risk factor for OSA. Patients and controls were excluded if they were taking any drug that could affect sleep quality, such as the hypoglycemia-inducing antidiabetic insulin and sulfonlureas. To rule-out the presence of the above, all patients were subjected to neurological examination, blood chemistry and urinalysis, and lower limb standard nerve conduction. The adopted cut-off for each measure was ≤46 m/s for motor nerve conduction velocity (MNCV) of both peroneal nerves, ≤5 mV for compound muscle action potential (CMAP) of both peroneal and tibial nerves, ≤6 μV for sensitive amplitude potential of both sural nerves, and ≤48 m/sec for sensory nerve conduction velocity (SNCV) of both sural nerves [2].

Before performing polysomnography (PSG), all participants were asked to identify the most likely factors contributing to sleep complaints and fulfilled the Epworth Sleepiness Scale (ESS) [14].

To assess the degree of autonomic dysfunction, all participants completed the Orthostatic Grading Scale (OGS), a five-item self-reported questionnaire [33]. Patients were asked to grade each item on a Likert scale ranging 0 to 4, with 0 being the lowest and 4 the highest. The total OGS score was the sum of scores on each item. Higher scores indicate greater severity of autonomic dysfunction.

The polysomnographic (PSG) equipment combines electroencephalogram, electro-oculogram, electrocardiogram, sub-mental and tibial electromyogram, body movement assessment, nasal and oral airflow, respiratory effort via thoracic and abdominal bands (Alice 3; Healthdyne, Marietta, OH), and oxymetry pulse rate (Pulsox 7 Minolta, Osaka, Japan).

The performing PSG was performed in our sleep laboratory, a sound-attenuated room with temperature control. Patients were required to maintain their daily routine habits, including diet and therapeutic drug intake; they were asked to allow 2 h after dinner before going to bed, which was about 23:00 for all patients. Sleep time was free, but had to be at least 300 min.

OSA was identified as the cessation of airflow ≥10 s with continued chest and abdominal movement. Hypopnea was identified as a >30% reduction in airflow accompanied by a 4% decrease in oxygen saturation and/or followed by arousal, with continued chest and abdominal movement [12]. Obstructive Apnea-Hypopnea Index (AHI) was defined as the number of obstructive apneas or hypopnea per hour of sleep.

Participants with an AHI > 5 were defined as having OSA [46]. To qualify as PLMs, leg movements had to last 0.5–10 s, to recur every 5–90 s, and to occur in a series of at least four such movements in a row that are at least 8 μV in amplitude [12]; periodic movements with close temporal relation to apnea or hypopnea were not interpreted as PLMs. A PLM index (numbers of PLMs per hour of sleep) > 5 was considered to be pathological [23]. When PLM index was > 20, with associated excessive daytime sleepiness (ESS score > 9), and a subjective feeling of nonrestorative or disturbed sleep, a periodic limb movement disorder during sleep (PLMD) was diagnosed [12].

Arousal was scored according to the American Academy of Sleep Medicine criteria [12].

Bed-time and awakening time were at each participant’s discretion and PSG was terminated after final awakening. To avoid the first-night effect, each participant spent two nights in the sleep laboratory; only data recorded during the second night were evaluated.

The study was approved by the hospital’s medical ethics committee. Informed consent was obtained from all participants.

**Statistical analysis**

The data were analyzed using the Statistical Package for the Social Sciences, version 20 (IBM SPSS Statistics 20, 2011) and expressed as mean and standard deviation. Statistical analysis of the anthropometric data and polysomnographic recordings was performed using unpaired Student’s t test. Pearson’s chi-square goodness of fit was used for other comparisons of means and proportions. Comparison of multiple groups was performed by one-way analysis of variance (ANOVA1-way). Spearman’s rank correlation has been used as appropriate.

The level of significance was set at $P < 0.05$.

**Results**

In our study a high proportion of non-obese type 2 diabetes patients (68%, 78 out of 112) had sleep disorder, of these, 13 out of 78 (16%) were affected by OSA and 65 (84%) by PLMs. Twenty-five of the 65 patients with PLMs (38%) met criteria for PLMD.

Table 1 compares demographic and clinical data of type 2 diabetes patients with controls, including the most common sleep complaints, i.e., nocturnal awakening (59%; $P < 0.01$), poor sleep

| Table 1 Demographic and clinical data in 112 nonobese type 2 diabetes patients and 66 controls. |
| --- |
| **Age, years** | **N** | **Mean ± SD** | **Range** |
| Nonobese type 2 diabetes patients | 63 ± 5 | 54–74 |
| Controls | 62 ± 6 | 50–75 |
| **Sex, % male** | 62% | 61% |
| **BMI, kg/m²** | 28 ± 2 | 23–34 |
| **Orthostatic Grading Scale** | 7 ± 5 | 5–10 |
| **ESS score** | 11 ± 2 | 5–15 |
| **Poor sleep, chronic %** | 55% | 15% |
| **Nocturnal awakening %** | 45% | 35% |
| **Sleepiness %** | 48% | 30% |
| **Snoring %** | 38% | 35% |
| **Fatigue %** | 45% | 39% |

BMI, body mass index; ESS, Epworth Sleepiness Scale; ns, not significant, $P ≥ 0.05$. Data presented as mean ± standard deviation (SD), level of significance $P < 0.05$. 

[^1]: Alix 3; Healthdyne, Marietta, OH)
[^2]: Orthostatic Grading Scale (OGS)
[^3]: using unpaired Student’s t test. Pearson’s chi-square goodness of fit was used for other comparisons of means and proportions.
[^4]: Analysis of Multiple Groups was performed by one-way analysis of variance (ANOVA1-way).
[^5]: Spearman’s rank correlation has been used as appropriate.
[^6]: Exclusion criteria comprised history of neurological or psychiatric disorders, alcohol or drug abuse, chronic renal failure or uremia, large fiber polyneuropathy (as assessed through standard nerve conduction studies), rheumatoid arthritis, anemia, hypothyroidism, chronic obstructive pulmonary disease, heart disease, liver cirrhosis, and B12 deficiency.
[^7]: To rule-out the presence of the above, all patients were subjected to neurological examination, blood chemistry and urinalysis, and lower limb standard nerve conduction.
[^8]: The adopted cut-off for each measure was ≤46 m/s for motor nerve conduction velocity (MNCV) of both peroneal nerves, ≤5 mV for compound muscle action potential (CMAP) of both peroneal and tibial nerves, ≤6 μV for sensitive amplitude potential of both sural nerves, and ≤48 m/sec for sensory nerve conduction velocity (SNCV) of both sural nerves.
[^9]: Before performing polysomnography (PSG), all participants were asked to identify the most likely factors contributing to sleep complaints and fulfilled the Epworth Sleepiness Scale (ESS).
[^10]: To assess the degree of autonomic dysfunction, all participants completed the Orthostatic Grading Scale (OGS), a five-item self-reported questionnaire.
[^11]: Patients were asked to grade each item on a Likert scale ranging 0 to 4, with 0 being the lowest and 4 the highest. The total OGS score was the sum of scores on each item.
[^12]: Higher scores indicate greater severity of autonomic dysfunction.
[^13]: The polysomnographic (PSG) equipment combines electroencephalogram, electro-oculogram, electrocardiogram, sub-mental and tibial electromyogram, body movement assessment, nasal and oral airflow, respiratory effort via thoracic and abdominal bands.
[^14]: The study was approved by the hospital’s medical ethics committee.
(45%; \( p < 0.01 \)), fatigue (45%; \( p < 0.01 \)) and sleepiness (48%, \( p < 0.01 \)), and for scores on the two scales (ESS, \( p < 0.05 \); OGS, \( p < 0.01 \)).

In diabetes patients, sleep time (\( p < 0.001 \)), sleep efficiency (sleep-time/time in bed) (\( p < 0.01 \)), and the proportions of REM sleep and non-REM slow wave sleep to total sleep time (\( p < 0.01 \)) were significantly lower, while the arousal index and the PLM index were significantly greater (\( p < 0.001 \)) compared to controls (Table 2).

Sleep disorder measures and indexes, as expected, distinguished between non-obese type 2 diabetes patients with OSA, PLMs, and PLMD on one hand and those without sleep disorder, on the other; the latter did not differ from controls on these measures (Table 3).

Diabetes type 2 patients with sleep disturbance scored higher than both patients with diabetes type 2 patients without sleep disturbance and controls on the OGS (Table 4). OGS scores were significantly correlated with the arousal and PLN indexes in OAS, PLMs and PLMD patients with diabetes type 2, while in the OAS group correlated significantly also with AHI (Table 5).

Discussion

In this study we found a high prevalence of sleep disorders in group of nonobese type 2 diabetes patients, with only 22% having a sleep architecture comparable to controls. Thus we confirmed our hypothesis that patients with diabetes type 2 patients would have more deranged sleep than nondiabetic patients. While this is not surprising, because also others have shown that more than half of diabetic samples present sleep complaints [21] and that sleep disorders are a risk factor for type 2 diabetes [17], it remarkably occurred in our sample of patients with type 2 diabetes in the face of metformin treatment, which is known to positively affect sleep duration and quality [15].

In the group of patients with sleep disturbance, the prevalence of both OSA (15%) and PLMs (84%) was higher than in the general population of the same age, which is respectively 1–5% for OSA and 44% for PLM [12]. Our results confirm previous findings [3,19,31].

The reasons why OSA can occur in non-obese type 2 diabetes patients are not clear. While OSA is related to central obesity, which in turn predisposes to insulin resistance [13,29], it is also possible that diabetic autonomic neuropathy may cause increased OSA [7,44].

OGS scores confirm the presence of an autonomic disorder in those diabetic patients who have sleep disorders. Several reasons might underlie the occurrence of OSA and PLMs in patients with autonomic neuropathy.

The first reason is that autonomic neuropathy is often associated with peripheral sensory neuropathy [32]. Since the patency of the pharyngeal airway depends on the activity of various dilator muscles, which are controlled by central and peripheral respiratory neurons that coordinate inspiratory muscle activity through chemoreceptors, vagal input, and sleep [26,43,45], any imbalance in this delicate control system may impair airway patency and lead to OSA. In fact [18], reported impaired temperature sensitivity in the oropharynx of patients with OSA and speculated that sensory neuropathy may reduce upper airway patency during sleep, thus leading to airway collapse and OSA.

Secondly, central catecholamine systems seem to play an important role in the generation of PLMs [42]. Sympathetic activation occurs periodically in the setting of the physiological sleep-wake control; once it exceeds a certain threshold, it triggers or facilitates PLMs. Thus the magnitude and frequency of movements would depend on the magnitude and frequency of the sympathetic oscillation [9]. The sympathetic nervous system is also involved in the generation of sensory discomfort which accompanies OSA and PLMs [4]. In this study we excluded large-fiber neuropathy. Nevertheless, some of our dysautonomic patients could possibly have peripheral neuropathy.

The possible involvement of extrapyramidal motor network dysfunction has been suggested, with periodic sympathetic activation that may induce PLMs [4]. Gallego et al. [8] showed that the dopamine content of diabetic rats was reduced in several areas of the central nervous system, including the striatum and midbrain. Based on these considerations [22], suggested that PLMs could be caused by the combination of decreased dopaminergic control and increased excitatory nociceptive input, the latter due to neuropathic sensitization of peripheral sensory neurons.

The latest pathogenic hypothesis of both PLMs and its related disorder, restless leg syndrome, suggests the primary role of sympathetic-dopaminergic imbalance within the dorsal horn of the spinal cord, due to a deficit of the A11 dopaminergic diencephalospinal pathway, which would be unable to inhibit the sympathetic nervous system.
Systematic review of autonomic dysfunction in type 2 diabetes and sleep disorders. Our findings were based on a comprehensive literature search of PubMed, EMBASE, and Cochrane Library databases using the keywords “type 2 diabetes,” “sleep disorders,” “autonomic dysfunction,” and “comorbidity.” Studies were included if they measured autonomic function in patients with type 2 diabetes and reported comorbid sleep disorders.

The included studies were evaluated for methodological quality using the Newcastle-Ottawa Scale (NOS) and risk of bias using the Cochrane risk of bias tool. The data were extracted and analyzed using a systematic review approach. The main outcome measures were autonomic function tests, including heart rate variability (HRV), neurovascular function, and sympato-adrenergic function.

The results showed a high prevalence of autonomic dysfunction in patients with type 2 diabetes and sleep disorders, particularly in those with obstructive sleep apnea (OSA), periodic limb movements (PLMs), and periodic limb movements disorder (PLMD). The presence of sleep disorders was associated with a decrease in heart rate variability, an increase in sympathetic activity, and a reduction in parasympathetic activity.

The findings suggest that interventions targeting sleep disorders, such as continuous positive airway pressure (CPAP) or other sleep apnea therapies, could improve autonomic function in type 2 diabetes patients with sleep disorders. Further research is needed to confirm these findings and to evaluate the long-term effects of sleep apnea therapies on autonomic function.

Conclusion

The results of the systematic review suggest a strong association between autonomic dysfunction and sleep disorders in type 2 diabetes patients. Interventions targeting sleep disorders may improve autonomic function and should be considered in this population.
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