Several studies indicate an association between obstructive sleep apnea syndrome (OSAS) and diabetic autonomic neuropathy (DAN). Observed frequency of OSAS in diabetic patients with DAN varies between 26% and 30%. Excessive daytime sleepiness is one of the major clinical symptoms of sleep disordered breathing. Diabetics with autonomic neuropathy might have abnormal control of respiration during sleep, probably resulting in a reduced daytime sleepiness. We investigated the impact of autonomic diabetic neuropathy on clinical symptoms (e.g., daytime sleepiness, measured by Epworth Sleepiness Scale, ESS) in patients with suspected OSAS. We examined 196 patients suspected of sleep apnea (52 female, 144 male, mean age 58.7 yrs, mean BMI 30.57 kg/m²). All patients underwent overnight polysomnography and were tested for autonomic neuropathy by a method of measuring heart rate variability and heart rate response to the Valsalva maneuver, standing and deep breathing using a computerized data analysis system. Eighty diabetic subjects: 52 DAN-, 28 DAN+; 116 subjects without diabetes: 101 without autonomic neuropathy (AN), 15 AN+. The group of diabetics with DAN+ had a mean apnoea/hypopnea index (AHI) of 38.6/h, mean oxygen desaturation: 77.5%, mean ESS-Score: 9.86. Diabetic patients DAN-: mean AHI:30.4/h, mean oxygen desaturation: 79.3 %, mean ESS-Score 9.73. Defining OSAS as AHI> 5/h and ESS-Score > 9, 46% of the diabetic patients DAN+ were positive, whereas in the DAN- group 61% met the criteria (non-diabetic patients without AN 50.5%; with AN : 60%). Although the group of diabetic patients with autonomic neuropathy had the lowest percentage of OSAS, statistical analysis showed no significance in comparisons between DAN-/DAN+ or diabetic/non-diabetic. In conclusion, although this study did not give statistical evidence, there is reason to assume that patients with diabetic autonomic neuropathy show fewer clinical symptoms of OSAS than those without it. The examination for OSAS might be indicated even without excessive daytime sleepiness because of elevated cardiovascular risk.

Key words: autonomic neuropathy, day time sleepiness, diabetes, obstructive sleep apnea syndrome
INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is defined as a repetitive collapse of the upper airways during sleep, leading to apnea or hypopnea with corresponding oxygen desaturations while respiratory effort persists (1). Respiratory disorders are followed by arousals. The consequence of the respiratory-induced sleep fragmentation is excessive daytime sleepiness, which is the major clinical symptom of patients with OSAS. The prevalence of OSAS in the middle-aged population ranges between 2% in women and 4% in men (2), with increasing numbers in the elderly population.

Several studies indicate an association between OSAS and diabetic neuropathy. Diabetes mellitus (DM) is one of the most common chronic diseases that affect the somatic and the autonomic nervous system (3, 4, 5, 6). Cardiovascular autonomic neuropathy in diabetic patients is associated with an increase in mortality (7, 8). There is also evidence that diabetes is a risk factor for mortality in patients with OSAS (9).

In previous studies, a relationship between OSAS and diabetic autonomic neuropathy (DAN) has already been assumed (10, 11, 12, 13). More recently Ficker et al (14) found OSAS in 26% of diabetics with DAN. Bottini et al (15) examined younger non-obese diabetics with DAN and found OSAS in 30% of cases, no differences were seen with regard to the severity of DAN.

The aim of this study was to investigate the impact of DAN on clinical symptoms of OSAS. Although diabetics with DAN might have abnormal control of respiration during sleep, and thus a higher risk for OSAS, the perception of clinical symptoms, e.g., sleepiness, might be reduced.

MATERIAL AND METHODS

Subjects

The study was approved by a local Ethics Committee. We examined patients suspected of OSAS admitted to our clinic, who gave their informed consent. The exclusion criteria were severe comorbidity, such as chronic heart failure, severe COPD, acute diabetic complications, dementia, dementia.

<table>
<thead>
<tr>
<th></th>
<th>DM-/AN-</th>
<th>DM-/AN+</th>
<th>DM+/AN-</th>
<th>DM+/AN+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>101</td>
<td>15</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>82 (81.2%)</td>
<td>13 (86.7%)</td>
<td>31 (59.6%)</td>
<td>18 (64.3%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (18.8%)</td>
<td>2 (13.3%)</td>
<td>21 (40.6%)</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53.7 ±10.1</td>
<td>57.1 ±7.7</td>
<td>65.0 ±10.2</td>
<td>65.5 ±8.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 ±4.9</td>
<td>32.4 ±4.4</td>
<td>30.9 ±5.0</td>
<td>30.8 ±4.8</td>
</tr>
</tbody>
</table>

Numbers are presented as absolute mean values ±SE or percent. DM - diabetes mellitus, DAN - diabetic autonomic neuropathy, BMI - body mass index.
alcoholism, drug abuse, and cardiac arrhythmia. One hundred ninety six patients were included: 52 females, 144 males; mean age 58.7 yr, mean BMI 30.57 kg/m$^2$. Eighty patients were diabetic, 28 of those were tested positive for DAN.

Sleep apnea

All patients underwent overnight polysomnography for the assessment of sleep disordered breathing by means of a computer-based system (Alice 4, Heinen and Loewenstein, Germany). Polysomnographic recordings included: electroencephalogram, electrooculogram, electromyogram of the chin, nasal and oral airflow (by thermistors), abdomen and chest movement, oxygen saturation (by finger probe), snoring (by microphone), body posture, and electrocardiogram. The data were analyzed on a visual basis by an experienced investigator. Sleep was defined according to the criteria of Rechtschaffen and Kales (16). Apnea was defined as a cessation of airflow for at least 10 s (17). Hypopnea was defined as a reduction in thoraco-abdominal movements of 50% or more and a decrease of the oxygen saturation of 4% or more. The apnea/hypopnea index (AHI) was calculated as the number of apneas and hypopneas per hour of total sleep time. Obstructive sleep apnea was defined as an AHI of 5 or more apneas/hypopneas per hour. Daytime sleepiness was measured by the Epworth Sleepiness Scale (18). A score of more than 9 points was considered as excessive daytime sleepiness. We defined the OSAS as a combination of AHI $\geq$5 and an ESS Score $>9$.

Autonomic neuropathy

Autonomic neuropathy was examined by standard cardiovascular tests with a computer-based system (Vagus 2100, Sigma, Germany): heart rate variability at rest and during deep breathing, heart rate response from lying to standing, and systolic blood pressure response were performed in accordance with the international standards (3). Test results were scored according to the normal age-dependent values provided with the software. Heart rate variation to the Valsalva test was rated separately, as patients with diabetic retinopathy could not participate. Patients with more than 2 pathological test results were considered positive for autonomic neuropathy. Patients with one or two pathological test results were excluded from the study as being inconclusive.

Statistical analysis was performed by means of the computer program SPSS using a $t$-test for independent groups, Levene’s test for equality of variances. A probability value of 0.05 was considered significant.

RESULTS

The 196 included subjects were divided into groups according to the presence or absence of DM and DAN. Data obtained in polysomnography were compared. Twenty eight of the 80 diabetic patients were identified positive for autonomic neuropathy (AN). Among the non-diabetics, 15 patients were positive for AN. The mean AHI in the group DM+/DAN- was 30.43/h, in the group DM+/DAN+ 38.6/h. The mean ESS Score for the group DM+/DAN- was 9.73 ±4.42, for DM+/DAN+ 9.86 ±4.48.

Among diabetics without DAN, 32 subjects (61.5%) met the criteria for OSAS, in the group of diabetics with DAN 13 subjects (46.4%).

The mean oxygen saturation (SaO$_2$) during sleep for all subjects was 92.5% with no significant differences between the four groups. The mean lowest oxygen
The main intention of this study was to investigate the impact of diabetes mellitus and autonomic diabetic neuropathy on clinical symptoms on daytime sleepiness in patients with suspected OSAS. Similarly to the occurrence of clinically asymptomatic myocardial infarction in diabetic patients with neuropathy, there might be a reduced awareness of excessive daytime sleepiness.

In our study, 35% of the diabetic patients were found to have autonomic neuropathy, whereas in the “Euro DIAB IDDM Complication Study” the
prevalence of autonomic neuropathy was 19.3% in the unselected group. This might point to the neuropathy as a selection factor for admittance to a sleep lab.

Patients with diabetes mellitus and autonomic neuropathy showed the highest mean AHI and 53.5% of them had an oxygen desaturation below 80% during sleep. In contrast, daytime sleepiness as measured by the Epworth Sleepiness Scale was increased only in 46.4% of the patients. Therefore, only 46.4% of the subjects within this group met the criteria for OSAS. In the group of diabetics without neuropathy, 61.5% were found to have OSAS. Diabetics with autonomic neuropathy seem to have a reduced perception of daytime sleepiness, although the objective criteria in this group are rather more severe.

Statistical analysis, however, showed no significant differences between the groups in regard to daytime sleepiness and AHI. Comparison between diabetics and non-diabetics and between subjects with and without neuropathy showed no significant differences either. Therefore, reduced clinical symptoms in patients with diabetes and autonomic neuropathy are possible, but our data gave no statistic evidence. One reason might that the number of the subjects was too small. As patients were admitted to our clinic because of suspected OSAS, a selection bias was a possibility. Further investigation would be required to resolve this issue.

In conclusion, although this study did not give statistical evidence, there is a reason to assume that patients with diabetic autonomic neuropathy show fewer clinical symptoms for OSAS than those without it. The examination for OSAS might be indicated even without excessive daytime sleepiness because of elevated cardiovascular risk.

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