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Obstructive sleep apnoea and diabetes mellitus: the role of cardiovascular autonomic neuropathy

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ABSTRACT: Knowledge of conditions associated with an increased prevalence of obstructive sleep apnoea (OSA) may help to identify patients with OSA and might give some insight into the pathogenesis of OSA and its sequelae. A number of earlier, smaller studies hinted at an association between diabetic cardiovascular autonomic neuropathy (AN) and OSA. The present study was, therefore, conducted with the aim of establishing the prevalence of OSA in diabetics with AN and of determining whether OSA is more prevalent in diabetics with AN, than in those without.

We studied two groups of diabetic patients: 23 with and 25 without AN. All patients were evaluated for possible OSA (apnoea/hypopnoea index Š10) using initial ambulatory screening followed by polysomnography.

Six patients with AN (26%) were found to have OSA, but none of the patients without AN met the diagnostic criteria ($p<0.01$). When the patients with OSA were compared to those without, no differences were found in terms of age, sex, body mass index or diabetes type or duration.

In conclusion, about one in four diabetic patients with autonomic neuropathy suffers from OSA. Thus, obstructive sleep apnoea is more prevalent in diabetic patients with autonomic neuropathy, than in those without.
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The prevalence of obstructive sleep apnoea (OSA) in the middle-aged population is about 2% in women and 4% in men [1]. However, there are some conditions associated with a distinctly higher prevalence of OSA. These include, for example, obesity, a family history of OSA, anatomically small pharyngeal airways and "primary" art-erial hypertension [2–4]. A more detailed knowledge of such conditions may help to identify patients at risk for OSA. Furthermore, a knowledge of such conditions might give some insights into the pathogenesis of OSA or its sequelae.

Cardiovascular autonomic neuropathy (AN) in diabetic patients is associated with increased mortality, and there has been some speculation that impaired neural control of breathing in diabetics with AN might lead to sleep-disordered breathing and, thus, contribute to the poor prognosis [5]. In addition, there is epidemiological evidence that diabetes is a risk factor for mortality in patients with sleep apnoea syndrome [6]. These epidemiological findings tend to support the hypothesis that AN might be associated with sleep-disordered breathing in some patients. A possible association between diabetic autonomic dysfunction and sleep apnoea has been under discussion for more than 20 yrs [7]. So far, two small studies have demonstrated a high prevalence of sleep-disordered breathing in patients with diabetic autonomic neuropathy [8, 9]. In another small study comparing diabetic patients with AN and those without, no differences in the numbers of apnoeic or hypoxaemic episodes were found [10], while a recent study demonstrated an increased number of desaturation episodes in diabetic patients with AN as compared with healthy controls [11]. Thus, there is still no clear evidence to show whether diabetic AN is indeed associated with OSA and, if so, what proportion of patients with diabetic AN suffer from OSA.

The present study was, therefore, carried out in an attempt to establish the prevalence of OSA in diabetic patients with AN and to determine whether OSA is more prevalent in diabetics with AN, than in those without.

Methods

Subjects

The study was designed to include 50 Caucasian patients with a history of diabetes mellitus of at least 5 yrs, 25 patients with AN and 25 patients without AN. All the patients were recruited from the out-patients department of our institution. As a first step, the patient files were screened consecutively by a single investigator to select patients fulfilling the inclusion criteria as defined below. This investigator was blinded to all information relating to

possible symptoms of OSA. Patients found to be eligible were informed of our intention to study nocturnal breathing in diabetic patients for scientific purposes. They were not aware of the hypothesis underlying our study, nor were they given any details about the symptoms of OSA. Consecutive patients who agreed to participate in the study were tested for AN, as defined below, and ass-igned either to a group positive for AN, or to a group negative for AN until at least 25 patients had been recruited to each group. All patients gave written informed consent and the study was approved by the Ethics Committee of Erlangen University.

Within a period of 10 months, during which a total of about 520 diabetic patients were seen in our out-patients department, 81 patients who fulfilled the inclusion criteria were identified. Of these, 65 agreed to take part in the study and underwent screening for AN. Thirty seven patients tested negative for AN and 25 patients positive, while in three patients the results were inconclusive (see below). To achieve equal numbers of patients in both groups, 12 randomly selected patients who had tested negative for AN were excluded. Two patients who had tested positive for AN decided to leave the study prior to screening for OSA. Thus, we finally investigated 23 patients with AN, and 25 patients without (table 1).

Inclusion criteria

All the patients had a history of diabetes mellitus of at least 5 yrs duration. Patients were excluded if: they had severe comorbidity (*e.g*. asthma, congestive heart failure); they had acute diabetic complications (*e.g.* ketoacidosis, hypoglycaemia, infection); they were receiving antihypertensive treatment; they had a history of cardiac or cerebrovascular disease; they had any other condition possibly associated with AN (*e.g*. alcoholism, uraemia, vitamin B12 deficiency); they admitted to regular use of alcohol, sedatives or hypnotics; or they had known OSA.

Definition of AN

All the patients underwent screening for AN in accordance with international standards [12] using a computer system (ProSciCard, MediSyst, Linden, Germany), as described elsewhere [13].

After a period of at least 5 min, heart rate variation (HRV) during normal breathing was measured in the supine and standing positions for 5 min each. From 150 artefact free R–R intervals the computer calculated the coefficient of variation (CV, the standard deviation of the distribution of R–R intervals divided by the mean), and the root mean squared successive difference (RMSSD) between adjacent R–R intervals as:

$$RMSSD = \sqrt{\frac{\sum_{i=1}^{k}((R-Ri+1)-(R-Ri))^2}{n}}$$

where $R–R_i$ = duration of i-th interval in milliseconds and n = number of R–R intervals. The subject, resting in the supine position, was then instructed to breathe deeply at a frequency of 6 cycles·min^{-1}. The inspiration and expiration intervals were 6 s and 4 s, respectively, with the breathing rhythm dictated by instructions on the computer screen. The CV and RMSSD were computed from 100 artefact-free R–R intervals. In the breathing cycle with the maximum HRV, the longest R–R interval ($R–R_{max}$) during expiration and the shortest R–R interval ($R–R_{min}$) during inspiration were determined to obtain the difference $R–R_{max}$ - $R–R_{min}$ (E–I difference) and the ratio $R–R_{max}$/$R-R_{min}$ (E/I ratio). After resting in the supine position for a further 5 min, the subject was asked to stand up quickly and remain standing while the first 40 consecutive heart beats were analysed. The change in position from lying to standing results in an increase in heart rate (HR) which peaks at about the 15th beat and is followed by a relative bradycardia that is most marked at about the 30th beat [14]. This characteristic HR response is usually expressed by the ratio of the R–R interval at the 30th beat and the R–R interval at the 15th beat in the standing position (30:15 ratio) [15]. ZIEGLER *et al*. [16] demonstrated that the shortest R–R interval occurs within beats 6–24 and the longest R–R interval within beats 21–39. Therefore, we used the modified maximum/minimum 30:15 ratio in this study, which was calculated as the longest R–R interval of beats 20–40 divided by the shortest R–R interval of beats 5–25, as recommended by ZIEGLER *et al.* [16].

For each patient, the seven parameters examined (CV at rest, RMSSD at rest, CV during deep breathing, RMSSD during deep breathing, E–I difference, E/I ratio and maximum/minimum 30:15 ratio) were compared automatically with published age-dependent normal values [16] by the software provided with the ProSciCard computer. The Valsalva manoeuvre was not used because of the risk of inducing retinal bleeding in patients with diabetic retinopathy. In accordance with published normal values, patients with three or more pathological tests were considered positive for AN [13]. Patients in whom none of the tests were pathological were considered to be negative for AN. In patients with one or two pathological tests, HRV testing was considered inconclusive, and these patients were excluded completely from the study.

Table 1. – Patient characteristics

	Autonomic neuropathy	
	Present	Absent
Subjects n	23	25
Age yrs	55.0±3.2	47.8±3.4
Sex F/M	11/12	12/13
Duration of diabetes yrs	20.7±2.1	14.6±1.7*
Type of diabetes I/II n	9/14	13/12
BMI kg·m^{-2}	25.2±0.9	25.1±0.9

Values are presented as absolute number or as mean±SEM. *: $p<0.05$, *versus* those with autonomic neuropathy. F: female; M: male; BMI: body mass index.

Diagnosis of sleep apnoea

All 48 patients underwent ambulatory screening for sleep apnoea with a digital recording device (MESAM 4;

Madaus-Schwarzer, Munich, Germany) developed to monitor oxygen saturation, HR, snoring, and body posture.

MESAM 4 recordings were scored with the computer-based automatic scoring system provided with the equipment, and the oxygen desaturation index was calculated. Patients with an hourly oxygen desaturation index of Š10, and who snored at least occasionally (identified by visual analysis of the MESAM 4 recordings), were admitted to our sleep laboratory and underwent polysomnography. Complete polysomnographic recordings were obtained, including oxygen saturation, nasal and oral air flow (measured by thermistors), chest movements, electroencephalogram, electromyogram of the chin and an electro-oculogram as required by the standards of the American Thoracic Society [17]. Data were stored in a computer-based sleep lab system ("SleepLab", CNS Inc., Minneapolis, MN, USA). The polysomnographic recordings were scored on the basis of visual analysis by experienced investigators blinded to the AN status of the patients. Sleep was defined in accordance with the criteria of RECHTSCHAFFEN and KALES [18]. Apnoea was defined as the cessation of airflow at the nose and mouth lasting for 10 s. Hypopnoea was defined as a decrease in thoracoabdominal motion Š50%, associated with a fall in baseline oxygen saturation Š4% [17, 19, 20]. The apnoea/hypopnoea index (AHI) was calculated as the number of apnoeas and hypopnoeas per hour of total sleep time. Obstructive apnoea was defined as the absence of nasal and oral airflow despite continuing respiratory effort. The obstructive apnoea/hypopnoea index (oAHI) was calculated as the number of obstructive apnoeas and obstructive hypopnoeas per hour of total sleep time. The central apnoea/hypopnoea index (cAHI) was calculated in the same way. To avoid false-negative results of polysomnography due to a "first night effect", all patients were studied for two consecutive nights. Patients with an oAHI of Š10 during the second polysomnographic recording were considered positive for obstructive sleep apnoea [21, 22].

Statistical analysis

All numbers are expressed as arithmetic mean±SEM. Group comparisons were performed using Fisher's exact test or the Mann-Whitney U-test. The statistical calculations were performed with the aid of SPSS (version 6.0.1; SPSS Inc., Chicago, IL, USA). For differences between groups, a two-tailed p-value of less than 0.05 was considered significant.

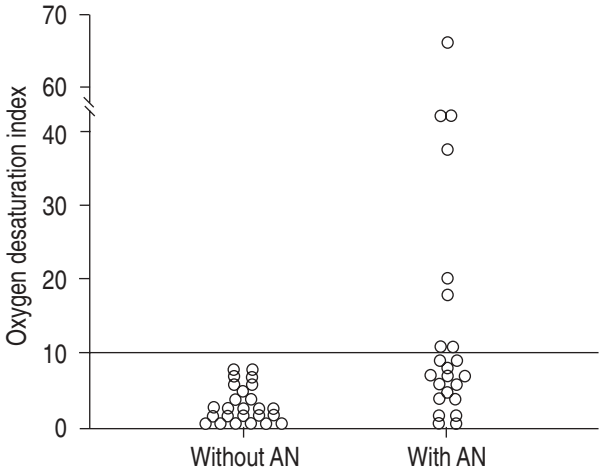

Fig. 1. – Oxygen desaturation indices of patients with and without autonomic neuropathy (AN). The horizontal line represents the cut-off, above which patients were admitted to the sleep laboratory.

Results

Ambulatory screening identified eight patients with an oxygen desaturation index of Š10, all of whom belonged to the group of patients with AN (fig. 1, table 2). On the basis of polysomnography, a diagnosis of OSA was made in six of these eight patients. The six patients had evidence of OSA as defined above in each of the two polysomnographic recordings. The remaining two patients did not meet the polysomnographic criteria for OSA as defined above. In the group without AN, ambulatory screening for OSA was negative in all patients. The difference in the prevalence of OSA between the two groups was significant ($p<0.01$). When the patients with OSA were compared with those who failed to meet the diagnostic criteria, no differences were found in terms of age, sex, BMI or the type or duration of diabetes (table 3).

Table 2. – Characteristics and results in patients screening positive for sleep apnoea

Patient No.	Age yrs	Sex	BMI kg·m^{-2}	Diabetes		Abnormal tests of HRV n	ODI	Polysomnography				
				Type	Duration yrs			AHI	oAHI	cAHI	$S_{a,O_2,min}$ %	OSA
1	64	F	20.8	II	15	5	42	32.4	25.5	6.9	78.2	+
2	72	M	22.6	II	10	4	11	2.0	2.0	0.0	93.2	-
3	53	M	23.8	I	35	6	38	26.6	25.1	1.5	84.7	+
4	60	F	37.5	II	19	6	18	13.5	13.5	0.0	73.5	+
5	43	M	33.0	II	17	6	66	62.3	60.5	1.8	65.6	+
6	60	F	26.3	II	26	4	42	57.8	53.1	4.7	74.6	+
7	64	F	27.2	II	28	6	11	7.6	7.5	0.1	85.9	-
8	51	M	24.0	II	9	6	20	21.8	19.8	2.0	86.2	+

BMI: body mass index; HRV: heart rate variation; ODI: oxygen desaturation index; AHI: apnoea/hypopnoea index; oAHI: obstructive AHI; cAHI: central AHI; $S_{a,O_2,min}$: minimum arterial oxygen saturation associated with apnoea or hypopnoea; OSA: obstructive sleep apnoea; F: female; M: male; I: diabetes type I; II: diabetes type II; +: present; -: absent.

Table 3. – Patient data related to presence or absence of sleep apnoea

	Obstructive sleep apnoea	
	Present	Absent
Subjects n	6	42
Age yrs	55.2±3.1	50.7±2.7
Sex female/male	3/3	20/22
Duration of diabetes yrs	20.2±3.7	17.1±1.5
Type of diabetes I/II	1/5	21/21
BMI $kg \cdot m^{-2}$	27.6±2.6	24.8±0.6

Values are presented as absolute number or as mean±SEM. There were no significant differences between the groups. For definitions see legend to table 2.

Discussion

In this study we used a two-stage approach to establish the prevalence of OSA in a group of diabetics with AN as compared to a group without AN. To determine reliable prevalence values it is essential to be sure of the sensitivity and specificity of the diagnostic methods used. The first diagnostic step consisted of ambulatory screening with MESAM 4. With respect to the group of patients with AN, the HRV index provided by MESAM 4 was not used for screening, as these patients had reduced HRV by definition, and could thus be expected to show false-negative results. A number of previous studies showed that manual analysis of MESAM 4 recordings for oxygen desaturation, HRV and snoring is superior to automatic scoring [23, 24]. With regard to the group of patients with AN, we did not use manual scoring in our screening procedure, as we were not sure that manual scoring based on all the signals provided by MESAM 4 would be as sensitive in patients with reduced HRV as it is in normal patients. Thus, our screening procedure was dependent solely on oximetry and snoring. Several studies have addressed the sensitivity and specificity of the oxygen desaturation index obtained with MESAM 4. Sensitivity values of 92–100% have been found when OSA was defined by a threshold value of 10 for the AHI obtained by polysomnography, but specificity has been shown by some studies to be poor [23, 25–27]. Patients with a positive screening test were thus studied subsequently by polysomnography as the diagnostic gold standard [28]. Our definition of apnoea was cessation of airflow for Š10 s. This is in accord with most authors and with international recommendations [17, 20], but there is considerable variation in the criteria used to identify hypopnoea. Hypopnoeas are often defined as a reduction in airflow by, for example, 50%, regardless of whether there is a decrease in oxygen desaturation or not [19]. As it is difficult accurately to quantify decrements in airflow using the relatively imprecise semiquantitative measuring systems usually employed in polysomnography, we decided to use as a definition of hypopnoea a combination of airflow reduction Š50% and an oxygen desaturation of Š4% [29]. This very strict definition corresponds with our screening procedure, and ensures that scoring of hypopnoeas can be reproduced precisely, which is essential to establish comparable prevalence values for OSA based on the AHI.

The overall sensitivity of our two-stage approach can be assumed to be at least 92% (the lowest published sensitivity value for oxygen desaturation index provided by MESAM 4). The overall specificity is 100% when polysomnography is regarded as the diagnostic gold standard and when OSA is defined by an AHI Š10. This diagnostic accuracy should, in principle, suffice to establish reasonably comparable prevalence values for the two groups studied.

In the group of diabetic patients with AN we found a significantly higher prevalence of OSA (26%) than in the group without AN (0%). Since other known risk factors for sleep apnoea, such as body mass index (BMI), age and sex were evenly distributed within the two groups, and the prevalence of OSA in the group with AN was much higher than in the general population [1], diabetic AN appears to be directly linked to sleep apnoea in the present group of patients.

In the group of diabetic patients with AN, the history of diabetes tended to be longer than in the group without AN (20.7±2.1 *versus* 14.6±1.7 yrs). This finding is in accordance with expectations, since patients with a longer history of diabetes have a significantly higher risk of developing AN [30, 31].

Five out of six patients with OSA had type II diabetes, while the nonapnoeic group contained equal numbers of patients with type I and type II diabetes. Because of the small sample size this difference was not statistically significant, but might indicate that AN in patients with type II diabetes is particularly associated with OSA.

The present results are largely in accord with the studies of Guilleminault *et al*. [32] and Mondini *et al.* [8], who reported a relationship between AN and sleep-related breathing abnormalities. Catterall *et al.* [10] compared breathing patterns and arterial oxygen saturation in eight diabetic subjects with symptomatic AN and eight diabetics without AN. The authors emphasized the fact that no differences in the numbers of apnoeic or hypoxaemic episodes were found. Unfortunately, they provided no precise information on the number of hypopnoeas, although they did observe that the majority of hypoxaemic episodes in their study were associated with hypopnoea. In their group of patients with autonomic neuropathy they reported "periods of irregular breathing" where "apnoea or hypopnoea occurred repetitively", lasting a mean of 34 min and a maximum of 103 min over a mean of 6.7 h of sleep. Assuming a frequency of only 1 $hypopnoea \cdot min^{-1}$ during these periods, some of the subjects probably had more than 10 hypopnoeas per hour, and today would be considered positive for OSA. The conclusions of Catterall *et al.* [10] are in contrast not only to our results obtained in a study sample that was three times as large, but also to the results of Rees *et al*. [9], who found evidence of OSA in three out of eight patients with AN compared with none of eight diabetic patients without AN. They are also in direct contrast to the results of Neumann *et al*. [11] who found an increased number of oxygen desaturation episodes in patients with AN as compared with normal controls.

Several mechanisms might serve to explain the occurrence of OSA in patients with AN. The central pathogenic factor in OSA is the collapse of the pharyngeal airway [33]. The patency of this segment of the airway is dependent largely on the activity of various pharyngeal dilator muscles [34]. The activity of inspiratory phasic dilator

muscles (*e.g*. genioglossus) as well as of tonic dilator muscles (*e.g*. tensor palatini) is controlled by central and peripheral respiratory neurones. The activity of these muscles is co-ordinated with the activity of the inspiratory muscles and is modulated by chemoreceptors, vagal input and sleep [35–37]. There is also increasing evidence of a local reflex mechanism that protects the airway from collapse during inspiration and is dependent on mechanoreceptors in the mucosa of the upper airway that are sensitive to different stimuli [38–40]. Topical oropharyngeal anaesthesia increases the pharyngeal resistance during sleep, and leads to an increased number of obstructive hypopnoeas and apnoeas during sleep in normal subjects and in snorers [41–43]. Larsson *et al*. [44] reported impaired temperature sensitivity in the oropharynx of patients with OSA as compared with age-matched nonsnoring control subjects. They speculated that this is due to a sensory neuropathy that might be associated with defective function of the local receptors supporting the patency of the upper airway during sleep. With this in mind it might be speculated that a condition such as AN, affecting many other autonomic neural systems and often associated with peripheral neuropathy [45], might also be associated with impairment of peripheral neurones responsible for dilating the upper airway, thus leading to upper airway collapse and OSA.

On the other hand, Veale *et al.* [46] have shown that OSA is associated with abnormal autonomic stress responses even when patients with diabetes, neurological disease and those taking drugs that might influence the results of autonomic testing, are excluded. Recently, they have also demonstrated that effective treatment of OSA with nasal continuous positive airway pressure (nCPAP) can lead to an improvement in these abnormal responses [47]. These findings indicate that our results may be open to a completely different interpretation, since they suggest that AN might be (at least to some extent) a consequence of OSA in those patients positive for AN and for OSA. Thus, OSA might have served as an additional risk factor for the development of AN in patients with diabetes.

In conclusion, we have demonstrated that about one in four diabetic patients with autonomic neuropathy suffers from obstructive sleep apnoea and that obstructive sleep apnoea is thus more prevalent in diabetic patients with autonomic neuropathy than in those without. The pathophysiological mechanisms underlying this association of autonomic neuropathy and obstructive sleep apnoea need to be studied further. Diabetics with autonomic neuropathy should be carefully evaluated for obstructive sleep apnoea.

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