Prevalence and predictive factors of sleep apnoea syndrome in type 2 diabetic patients

J.-P. Laaban\textsuperscript{a}, S. Daenen\textsuperscript{b}, D. Léger\textsuperscript{c}, S. Pascal\textsuperscript{a}, V. Bayon\textsuperscript{c,∗}, G. Slama\textsuperscript{b}, F. Elgrably\textsuperscript{b}

\textsuperscript{a}Service de pneumologie, Hôtel-Dieu de Paris, université Paris-Descartes, AP–HP, Paris, France
\textsuperscript{b}Service de diabétologie, Hôtel-Dieu de Paris, université Paris-Descartes, AP–HP, Paris, France
\textsuperscript{c}Centre du sommeil et de la vigilance, centre de référence hypersomnies rares, Hôtel-Dieu de Paris, université Paris Descartes, AP–HP, 1, place du Parvis-Notre-Dame, 75181 Paris, France

Received 3 September 2008; received in revised form 4 March 2009; accepted 9 March 2009
Available online 15 August 2009

Abstract

\textbf{Aim.} – This study aimed to assess the prevalence and characteristics of sleep apnoea syndrome (SAS) in patients hospitalized for poorly controlled type 2 diabetes.

\textbf{Methods.} – An overnight ventilatory polygraphic study was systematically performed in 303 consecutive patients.

\textbf{Results.} – Overall, 34\% of these patients had mild SAS, as defined by a respiratory disturbance index (RDI) of 5–15; 19\% had moderate SAS (RDI: 16–29) and 10\% had severe SAS (RDI ≥ 30). The SAS was obstructive in 99\% of the apnoeic patients. The percentage of patients with excessive daytime sleepiness (Epworth sleepiness scale > 10), fatigue or nocturia did not significantly differ among patients with severe, moderate or mild SAS versus non-apnoeic patients. The percentage of patients who snored was significantly higher in patients with severe or moderate SAS versus non-apnoeic patients. HbA1c, duration of diabetes and the prevalences of microalbuminuria, retinopathy and peripheral neuropathy did not significantly differ among patients with severe, moderate or mild SAS versus non-apnoeic patients. However, patients with severe or moderate SAS had significantly higher values for body mass index, waist circumference and neck circumference than non-apnoeic patients.

\textbf{Conclusion.} – In type 2 diabetic patients with poor diabetic control, obstructive SAS is highly prevalent and related to abdominal obesity, and should be systematically screened for, as it cannot be predicted by the clinical data.

© 2009 Elsevier Masson SAS. All rights reserved.

Keywords: Obstructive sleep apnoea syndrome; Type 2 diabetes; Obesity

Résumé

Prévalence et facteurs prédictifs de syndrome d’apnées du sommeil chez des patients présentant un diabète de type 2.

\textbf{Objectifs.} – Évaluer la prévalence et les caractéristiques du syndrome d’apnées du sommeil (SAS) chez des patients hospitalisés pour un diabète de type 2 mal équilibré.

\textbf{Méthodes.} – Une polygraphie ventilatoire a été réalisée chez 303 patients consécutifs.

\textbf{Résultats.} – Trente-quatre pour cent des patients avaient un SAS léger défini par un index d’apnées-hypopnées (IAH) entre 5 et 15, 19\% un SAS modéré (IAH: 16–29) et 10\% un SAS sévère (IAH ≥ 30). Il s’agissait d’un SAS obstructif dans 99\% des cas. Le pourcentage des patients présentant une somnolence diurne excessive (score d’Epworth > 10), une fatigue ou une nycturie ne différait pas significativement entre les patients ayant un SAS sévère, modéré ou léger et les non apnéiques. Le pourcentage de ronfleurs était significativement plus élevé chez les patients ayant un SAS sévère ou modéré que chez les non apnéiques. L’HbA1c, l’ancienneté du diabète et la présence d’une microalbuminurie, d’une rétinopathie et d’une neuropathie périphérique ne différaient pas significativement entre les patients ayant un SAS sévère, modéré ou léger et les non apnéiques. Les patients qui avaient un SAS sévère ou modéré avaient un indice de masse corporelle, un tour de taille et un périmètre cervical significativement plus élevés que les non apnéiques.

∗ Corresponding author.
E-mail address: virginie.bayon@htd.aphp.fr (V. Bayon).
The prevalence of type 2 diabetes has dramatically increased over the past few years in Western countries mainly because of the obesity epidemic [1]. In the United States, diabetes is clinically diagnosed in 5.9% of adults [1] while the prevalence is around 3% in France and more than 90% of diabetics are type 2 [2,3].

Type 2 diabetes has also been reported to be much more prevalent in patients with obstructive sleep apnoea syndrome (SAS) than in non-apnoeic male snorers [4,5]. However, the relationship between the type 2 diabetes and obstructive SAS epidemics remains controversial, despite the fact that the two diseases share similar risk factors—in particular, obesity and visceral adiposity [6–8]. West et al. found a prevalence of obstructive SAS of 23% in a large group of men with type 2 diabetes [7]. However, in that study, SAS was objectively assessed by polygraphy based on oximetry tracings from only a small sample of subjects. Among the subjects included in the Sleep Heart Health Study, the prevalence of SAS was significantly higher in diabetic than in non-diabetic patients, although the obstructive apnoea index did not differ between them, and the prevalence of central apnoea and periodic breathing was also higher in diabetic than in non-diabetic subjects [8]. Indeed, a better understanding of the interaction between SAS and type 2 diabetes may have important public health implications.

Several studies have demonstrated that obstructive SAS is associated with insulin resistance and glucose intolerance independent of obesity [9–11], and the severity of intermittent hypoxaemia has been correlated with impaired glucose metabolism. In contrast, suppression of sleep apnoea was reported to improve glycaemic control in patients with type 2 diabetes [12]. Thus, given the theoretical possibility that untreated SAS might be contributing to poor control of diabetes, we routinely performed systematic screening for SAS, using nocturnal respiratory polygraphy in patients with poorly controlled type 2 diabetes.

The objective of the present study was to evaluate the prevalence of undiagnosed SAS in patients with type 2 diabetes hospitalized for poor diabetic control. Another goal of the study was to assess the characteristics of SAS in such patients in terms of type, severity, symptoms and risk factors.

1. Materials and methods

1.1. Study population

Participation in the present study was proposed to all patients admitted over a 6-month period—from January to June 2007—to the Department of Diabetology at our hospital with poorly controlled type 2 diabetes, as assessed by one hospital staff doctor during an outpatient visit. The diabetic patients found to be poorly controlled (based on clinical and biological data) were hospitalized for an average of 1 to 5 days for various clinical examinations and patient education.

Every hospitalized patient was included regardless of age or gender, presence or absence of SAS symptoms, severity of obesity and presence of any associated cardiovascular diseases. All included patients were informed that they would be diagnosed for sleep apnoea during their hospitalization and that their doctor would be informed of the results. However, patients who had already been diagnosed or treated for sleep apnoea were not included or recorded, as were also those who had heart failure, severe valvular disease, severe renal failure and unstable cardiac or respiratory disease.

All investigations were performed according to the ethics guidelines of the institution to protect the rights of the patient (authorized information and approbation, and protection of anonymity of the data approved by the Commission nationale informatique et liberté [CNIL]).

1.2. Nocturnal respiratory polygraphic study

A nocturnal respiratory polygraphic study using analyses of nasal airflow, tracheal sounds and oximetry (CID® 102, Cidelec, Angers, France) was carried out for one night per study subject during hospitalization in a conventional diabetic ward. A microphone was placed above the sternal notch. Several signals were derived from the microphone according to their energy and frequency, including tracheal sounds during normal breathing and during snoring, and any variations in suprasternal pressure.

In accordance with international classification guidelines, apnoea was defined as the complete cessation of airflow for at least 10 s. Apnoea was classified as ‘obstructive’ in the presence of respiratory efforts during the apnoea as detected by an increased variation in suprasternal pressure [13]. Apnoea was classified as ‘central’ in the absence of respiratory efforts and ‘mixed’ when it began with central and ended with obstructive apnoea. Hypopnoea was defined as a decrease of greater or equal to 50% in the nasal pressure signal, associated with oxygen desaturation greater or equal to 4% lasting for at least 10 s. The respiratory disturbance index (RDI) was calculated as the total number of apnoea and hypopnoea events per hour of recording. Mild SAS was defined as an RDI between 5 and 15, moderate SAS as an RDI between 16 and 29 and severe SAS as an RDI greater or equal to 30. Several parameters of nocturnal oxyhaemoglobin desaturation were computed, including the mean nocturnal SaO2, percentage of recording time spent at SaO2 less than 90% and percentage of recording time spent at SaO2 less than 80%, and the oxyhaemoglobin desaturation index (ODI) was defined as the number of episodes of oxyhaemoglobin desaturation greater or equal to 4% per hours of
recording. Obstructive SAS was defined as the percentage of obstructive and mixed apnoeic episodes greater than 50% of the total number of apnoeic episodes. Central SAS was defined as the percentage of central apnoeic events greater than 50% of the total number of apnoeic events.

1.3. Clinical data

To assess SAS symptomatology, patients were questioned about their snoring, fatigue and nocturia at the time of admission. Patients also completed the Epworth sleepiness scale (ESS) [14] to better describe their sleepiness. Excessive daytime sleepiness was defined as an ESS score greater than 10.

Retinopathy, peripheral neuropathy and hypertension were reported as either a ‘yes’ or ‘no’ in the patient’s file. The following data were also recorded: HbA1c; antidiabetic treatment (insulin or oral antidiabetic agents); duration of diabetes; microalbuminuria; weight; height; body mass index (BMI); and waist and neck circumferences.

The presence of the metabolic syndrome was determined according to the criteria of the American Heart Association/National Heart, Lung, and Blood Institute [15].

1.4. Statistical methods

All numerical variables are expressed as mean ± S.D. Comparisons of categorical and numerical variables were made between non-apnoeic patients and patients with mild SAS, between non-apnoeic patients and patients with moderate SAS and between non-apnoeic patients and patients with severe SAS. The χ² test was used for comparisons of categorical variables between groups and Student’s t-test was used for comparisons of numerical variables between groups. A P-value of less than 0.05 was considered statistically significant.

2. Results

A total of 362 patients with type 2 diabetes were hospitalized during the study period because of poor diabetic control, of which 23 (6%) had already been diagnosed with sleep apnoea. Thirty-two patients fulfilled the exclusion criteria and were excluded. Also, in four cases, it was impossible to analyze the polygraphy due to technical failure. The remaining 303 patients (156 men, 147 women) were finally included in the study.

The prevalence of newly diagnosed SAS was 63% (191/303) in these patients. The SAS was obstructive in 99% and only one patient had central SAS. The prevalences of severe, moderate and mild SAS were 10% (31/303), 19% (57/303) and 34% (103/303), respectively. The sleep respiratory parameters are summarized in Table 1.

The percentage of patients with excessive daytime sleepiness (ESS >10), fatigue or nocturia did not significantly differ between patients with severe, moderate or mild SAS versus non-apnoeic patients (Table 1). However, the percentage of patients who snored was significantly higher in those with severe or moderate SAS versus non-apnoeic patients, while the prevalence of hypertension was significantly higher in patients with severe SAS than in non-apnoeic patients, but did not differ between patients with moderate or mild SAS versus non-apnoeic patients (Table 1).

There was no significant difference between patients with severe, moderate or mild SAS versus non-apnoeic patients in terms of diabetes characteristics such as HbA1c, duration and treatment of diabetes, and prevalences of microalbuminuria, retinopathy and peripheral neuropathy (Table 2). However, the prevalence of the metabolic syndrome was significantly higher in patients with severe, moderate or mild SAS versus non-apnoeic patients (Table 2).

Age did not significantly differ between patients with severe, moderate or mild SAS versus non-apnoeic patients (Table 3), whereas the percentage of males was significantly higher in those with moderate or mild SAS versus non-apnoeic patients, but did not differ between severe SAS and non-apnoeic patients (Table 3).

Patients (both men and women) with severe or moderate SAS had significantly higher BMI values, and waist and neck circumferences, compared with non-apnoeic patients. In addition, men with mild SAS had significantly higher BMI values, and waist and neck circumferences, compared with non-apnoeic patients.
values and waist circumference than non-apnoeic men. In women, however, BMI values, waist circumference and neck circumference did not significantly differ between the mild SAS and non-apnoeic patients (Table 3).

3. Discussion

In the present study, we systematically performed nocturnal respiratory polygraphic studies in 303 patients consecutively admitted to hospital because of poorly controlled type 2 diabetes. We found that the prevalence of previously undiagnosed SAS was high in these patients, reaching 63%. Also, nearly all of the apnoeic patients had the obstructive form of the condition, whereas the prevalence of obstructive SAS in the general population is much lower, ranging from 2 to 9% [16]. In addition, high prevalences of obstructive SAS have been reported in patients with congestive heart failure, coronary artery disease, stroke and/or hypertension [17–19].

To our knowledge, only two previous studies have assessed the prevalence of SAS in patients with type 2 diabetes. West et al. reported that the prevalence of SAS was 23% in a cohort of 938 type 2 diabetic men who answered the Berlin questionnaire designed to screen for likely SAS [6]. The diagnosis of SAS was based on overnight home oximetry, completed as part of a home sleep study of those patients in whom oximetry suggested a diagnosis of SAS. A limitation of the study was that screening oximetry was only performed in a sample of 240 patients, comprising 124 patients whose questionnaire scores suggested a high risk of SAS and 116 who were scored as low risk. This means that the reported prevalence of SAS was not a true prevalence, but an extrapolation from oximetry data from responders to the questionnaire.

In contrast, in our present study, all patients underwent an in-hospital polygraphic study regardless of the presence or absence of symptoms suggestive of SAS. Analysis of baseline data from the Sleep Heart Health Study showed that the RDI was greater than 15 events per hour in 23.8% of the 470 participants with diabetes (P<0.001), and all subjects underwent an overnight home polysomnography test [8]. However, the obstructive apnoea index did not differ between diabetic and non-diabetic participants. The prevalence of central apnoea was higher in diabetic than in non-diabetic participants, but remained low (<5%) overall.

One limitation of the Sleep Heart Health Study is that the diagnosis of diabetes was based on self-reported diabetes, which may have resulted in misclassification or underreporting of diabetes status. In our study, the diagnosis of diabetes was based on overnight home oximetry, completed as part of a hospital polygraphic study regardless of the presence or absence of symptoms suggestive of SAS. Analysis of baseline data from the Sleep Heart Health Study showed that the RDI was greater than 15 events per hour in 23.8% of the 470 participants with diabetes (P<0.001), and all subjects underwent an overnight home polysomnography test [8]. However, the obstructive apnoea index did not differ between diabetic and non-diabetic participants. The prevalence of central apnoea was higher in diabetic than in non-diabetic participants, but remained low (<5%) overall.

Table 2
Characteristics of diabetes in the study patients with no, mild, moderate and severe SAS.

<table>
<thead>
<tr>
<th>Group I RDI &lt; 5 (n = 112)</th>
<th>Group II RDI 5–15 (n = 103)</th>
<th>Group III RDI 16–29 (n = 57)</th>
<th>Group IV RDI ≥ 30 (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>9.1 ± 1.8</td>
<td>9.2 ± 1.8</td>
<td>9.1 ± 1.8</td>
<td>9.3 ± 1.8</td>
</tr>
<tr>
<td>HbA1c &gt; 7% (%)</td>
<td>87</td>
<td>87</td>
<td>90</td>
<td>84</td>
</tr>
<tr>
<td>Insulin (%)</td>
<td>46</td>
<td>46</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Duration of insulin (years)</td>
<td>3 ± 5</td>
<td>4 ± 6</td>
<td>4 ± 6</td>
<td>4 ± 4</td>
</tr>
<tr>
<td>Oral antidiabetics (%)</td>
<td>63</td>
<td>61</td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>13 ± 10</td>
<td>16 ± 9</td>
<td>14 ± 11</td>
<td>15 ± 11</td>
</tr>
<tr>
<td>μalb &gt; 30 mg/24 h (%)</td>
<td>25</td>
<td>34</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>66</td>
<td>48</td>
<td>53</td>
<td>68</td>
</tr>
<tr>
<td>Peripheral neuropathy (%)</td>
<td>42</td>
<td>46</td>
<td>45</td>
<td>56</td>
</tr>
<tr>
<td>Metabolic syndrome (%)</td>
<td>57</td>
<td>74</td>
<td>76</td>
<td>78</td>
</tr>
</tbody>
</table>

RDI: respiratory disturbance index; μalb: microalbuminuria; a: group I versus group II; b: group I versus group III; c: group I versus group IV; 1P<0.001; 2P<0.01; 3P<0.05; 4ns: non-significant difference.

Table 3
Clinical characteristics in the study patients with no, mild, moderate and severe SAS.

<table>
<thead>
<tr>
<th>Group I RDI &lt; 5 (n = 112)</th>
<th>Group II RDI 5–15 (n = 103)</th>
<th>Group III RDI 16–29 (n = 57)</th>
<th>Group IV RDI ≥ 30 (n = 31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 12</td>
<td>60 ± 11</td>
<td>63 ± 10</td>
<td>62 ± 13</td>
</tr>
<tr>
<td>Men (%)</td>
<td>40%</td>
<td>55%</td>
<td>68%</td>
<td>48%</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.5 ± 15.9</td>
<td>87 ± 15.9</td>
<td>91.6 ± 15.3</td>
<td>97.4 ± 21.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.1 ± 4.9</td>
<td>31.1 ± 4.9</td>
<td>32.7 ± 9.1</td>
<td>35.2 ± 6.7</td>
</tr>
<tr>
<td>BMI, men (kg/m²)</td>
<td>27.6 ± 4.5</td>
<td>30.4 ± 4.8</td>
<td>32.1 ± 10.4</td>
<td>33.5 ± 6.9</td>
</tr>
<tr>
<td>BMI, women (kg/m²)</td>
<td>30.2 ± 4.9</td>
<td>32 ± 5</td>
<td>34 ± 4.8</td>
<td>36.8 ± 6.4</td>
</tr>
<tr>
<td>Waist circumference, men (cm)</td>
<td>97 ± 14</td>
<td>107 ± 15</td>
<td>109 ± 14</td>
<td>124 ± 17</td>
</tr>
<tr>
<td>Waist circumference, women (cm)</td>
<td>99 ± 15</td>
<td>105 ± 12</td>
<td>109 ± 13</td>
<td>113 ± 16</td>
</tr>
<tr>
<td>Neck circumference, men (cm)</td>
<td>40.4 ± 3</td>
<td>42.2 ± 6.2</td>
<td>43.5 ± 2.8</td>
<td>46.1 ± 4.3</td>
</tr>
<tr>
<td>Neck circumference, women (cm)</td>
<td>36.1 ± 3.4</td>
<td>37.7 ± 3.2</td>
<td>39.2 ± 3.6</td>
<td>39.7 ± 4.1</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>12</td>
<td>15</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

BMI: body mass index; a: group I versus group II; b: group I versus group III; c: group I versus group IV; 1P<0.001; 2P<0.01; 3P<0.05; 4ns: non-significant difference.
An absence of subjective sleepiness was observed in 65% of patients with SAS. Whereas most patients (87%) had increased HbA1c levels, the level did not differ between apnoeic and non-apnoeic patients, whereas those with severe or moderate SAS had higher BMI values than the non-apnoeic diabetics, with differences observed in both male and female patients. In the Sleep Heart Health Study, the difference in RDI between diabetic and non-diabetic participants was not confirmed after accounting for obesity [8]. In obese patients, the prevalence of SAS is very high, especially in those with massive or abdominal obesity [21–23]. In contrast, in our study, only 8% of the patients with type 2 diabetes were massively obese, although those with severe or moderate SAS had larger waist and neck circumferences than the non-apnoeic patients, which suggests that the high prevalence of SAS in our diabetic patients was mainly related to abdominal obesity.

Several studies have shown that the prevalence of obstructive SAS is higher in diabetic patients with autonomic neuropathy than in those without [24,25]. Autonomic neuropathy may be associated with an impaired central control of breathing that could lead to instability of the upper airways during sleep. However, in the present study, autonomic neuropathy was not systematically screened for.

Obstructive SAS may be one of the factors that contribute to poor diabetes control, which could account for the high prevalence of SAS in our study, as we included only patients with poorly controlled diabetes. Furthermore, intermittent hypoxaemia and sleep fragmentation can lead to greater alterations in glucose metabolism through several potential mechanisms, including: sympathetic hyperactivity resulting in increased glycogen breakdown and gluconeogenesis; increased cortisol production; release of inflammatory cytokines (interleukin-6 and tumour necrosis factor); and increased leptin production [26]. West et al. found a significant correlation between the desaturation index and HbA1c in men with type 2 diabetes recruited from a hospital database [7]. In our study, the HbA1c level did not differ between apnoeic and non-apnoeic patients, whereas most patients (87%) had increased HbA1c levels.

The effects of sleep apnoea treatment on glucose metabolism remain a controversial issue. In patients with type 2 diabetes and obstructive SAS, Babu et al. demonstrated that continuous positive airway pressure (CPAP) therapy improves glycaemic control [12]. However, the study was not randomized and did not include a control group receiving sham CPAP therapy. Several studies failed to demonstrate any improvement in insulin sensitivity following CPAP therapy in patients with SAS, however, most of the patients included in these studies were not diabetic [26,27].

One important finding of the present study is that most patients with SAS do not complain of excessive daytime sleepiness. An absence of subjective sleepiness was observed in 65% of the patients with severe SAS, in 85% of those with moderate SAS and in 74% of those with mild SAS. Comparable results have been reported in patients with obstructive SAS associated with systolic heart failure [28]. The prevalence of excessive daytime sleepiness did not differ between apnoeic and non-apnoeic patients. A high proportion of non-apnoeic patients complained of snoring, nocturia and fatigue. These results highlight the difficulties of SAS screening in patients with type 2 diabetes, as the classical symptoms of SAS are neither sensitive nor specific in such a patient population.

Type 2 diabetic patients also have a high risk of developing coronary artery or cerebrovascular disease [29]. In addition, it has been well established that obstructive SAS increases the risks of hypertension, coronary artery disease, stroke and fatal cardiovascular events [15,16,30,31]. The presence of obstructive SAS is, therefore, likely to increase the cardiovascular risk in patients with type 2 diabetes. Based on these data, we consider it important to look for sleep apnoea in type 2 diabetics on a more regular basis. Moreover, it has been shown that the treatment of severe SAS with CPAP is associated with a reduced risk of both fatal and non-fatal cardiovascular events [31].

Type 2 diabetes is an important component of the metabolic syndrome, which is associated with increased incidences of cardiovascular disease and cardiovascular-related mortality [32]. It has also been shown that obstructive SAS is independently associated with an increased prevalence of the metabolic syndrome [33]. In the present study, the prevalence of the metabolic syndrome was higher in patients with SAS of any severity compared with non-apnoeic patients.

Diabetes is independently associated with impaired pulmonary function and, especially, a decreased vital capacity, demonstrated to be an independent predictor of type 2 diabetes [34,35]. Our study did not include pulmonary function tests, but it would be of interest to evaluate whether or not a decreased vital capacity is associated with the presence of obstructive SAS in diabetic patients.

In conclusion, we have shown that the prevalence of undiagnosed obstructive SAS is high among patients with poorly controlled type 2 diabetes and that it is mainly related to abdominal obesity. Also, we have found that the presence of obstructive SAS cannot be predicted by clinical data, which suggests that SAS should be systematically screened for in such a patient population.

4. Conflicts of interests

The authors do not have any conflict of interests to declare regarding the present study.

References


