Newly diagnosed obstructive sleep apnoea and type 2 diabetes mellitus

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ABSTRACT

INTRODUCTION: Obstructive sleep apnoea (OSA) is frequent in type 2 diabetes mellitus (DM) and is seen in 12-30% of patients with newly diagnosed OSA according to previous studies. Our aim was to determine the referral pattern and prevalence of patients with self-reported type 2 DM in a Danish cohort of patients with newly diagnosed OSA. Furthermore, we compared clinical data related to the sleep disorder in patients with and without type 2 DM and different OSA severities.

METHODS: This retrospective observational study was based on data from a cohort including all patients offered continuous positive airway pressure therapy in the course of a 14-month period after being referred to a sleep disorders clinic.

RESULTS: A total of 54 of 696 (7.8%) patients had type 2 DM. The majority of the patients in the type 2 DM group were referred from a general practitioner and only 8% from diabetes clinics. BMI, age and cardiovascular morbidity in type 2 DM patients were significantly higher than in the group without diabetes, while the Epworth Sleepiness Scale (ESS) score, the Apnea Hypopnea Index (AHI) and the Oxygen Desaturation Index (ODI) were not statistically different. Daytime sleepiness was similar in patients with mild-to-moderate compared with severe OSA.

CONCLUSIONS: AHI, ESS and ODI were similar in type 2 DM and the non-diabetic group. The prevalence of type 2 DM was lower than expected. Attention of healthcare providers to the association between type 2 DM and OSA is needed.

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Obstructive sleep apnoea (OSA) is characterized by episodes of partial or complete obstruction of the upper airways during sleep. This leads to sleep fragmentation and repetitive desaturation, snoring and daytime sleepiness, and patients with OSA share many of the risk factors for developing type 2 diabetes, including obesity and age [1, 2]. The two conditions interact although the precise pathophysiological link between insulin resistance and OSA remains unclear [3]. Several studies report a much higher prevalence of OSA in type 2 diabetes mellitus (DM) than in the background population [4-9], which in 2008 prompted the International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention to recommend that clinical practice should reflect the close association between OSA and diabetes [10]. However, it remains unclear if this recommendation is being followed in daily clinical life.

The primary aim of this retrospective study was to determine the prevalence of patients with self- reported type 2 DM among patients with newly diagnosed OSA referred to a sleep disorder clinic in Denmark. In addition, the study describes the referral pattern and compares clinical data related to the sleep disorder in patients with and without diabetes and different OSA severities.

METHODS

This study is based on a cohort including all patients offered positive airway pressure (CPAP) therapy during the 14-month period from 1 January 2012 to 28 February 2013 as a result of newly diagnosed OSA after being referred to an outpatient sleep disorders clinic in Silkeborg, the Central Denmark Region, Denmark. The clinic offers free-of-charge ambulatory diagnostic cardio respiratory monitoring (CRM) and CPAP treatment including regular follow-ups. Both primary physicians and hospital departments refer patients with OSA to the clinic, which is the largest of its kind in the region (1.27 mill. inhabitants). Patients with central sleep apnoea with a need for bi-level positive airway pressure are referred to the regional university clinic. In Denmark, physicians traditionally refer patients with suspected OSA to an otorhinolaryngeal specialist who, in turn, can refer the patients to the clinic for sleep-related disorders, in some cases (29.6%) preceded by a diagnostic CRM with various equipment. Diagnostic monitoring of respiratory flow, thoracic movements and transcutaneous oxygen saturation was performed in the clinic with a Philips Stardust II Sleep Recorder for the remaining 70.4% of the patients and data were analyzed using Alice PDX software.

The patients filled out a questionnaire regarding sleep-related symptoms, medical history, medication, smoking, height, weight and Epworth Sleepiness Scale (ESS) score to quantify daytime sleepiness. The otorhinolaryngeal specialist supplemented the questionnaire with problem-focused questions centered on

ORIGINAL ARTICLE

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TABLE 1

Clinical characteristics of patients with newly diagnosed obstructive sleep apnoea.

	All patients			5 < AHI < 30			AHI ≥ 30		
	no DM (N = 636)	T2DM (N = 54)	p-value	no DM (N = 314)	DM (N = 24)	p-value	no DM (N = 322)	DM (N = 30)	p-value
Male, n (%)	475 (75)	41 (76)	NS	215 (68)	15 (58)	NS	260 (81)[a]	26 (87)[b]	NS
Age, yrs, mean ± SD	53 ± 12	60 ± 11	< 0.001	52 ± 12	58 ± 11	0.08	54 ± 12	61 ± 11	< 0.01
Body weight, kg, mean ± SD [N_{alt}]	96 ± 22 [603]	105 ± 23 [53]	< 0.01	91 ± 20 [297]	108 ± 26 [23]	< 0.01	101 ± 23[a] [306]	103 ± 20	NS
BMI, kg/m^2, mean ± SD [N_{alt}]	30.7 ± 6.8 [599]	34.4 ± 6.9 [53]	< 0.001	29.3 ± 5.9 [293]	35.0 ± 8.0 [23]	< 0.01	32.0 ± 6.4[a] [306]	34.1 ± 6.1	0.09
HbA_{1c}, mmol/mol, mean ± SD (%) [N_{alt}]	–	55 ± 13 (7.1 ± 1.2) [51]	–	–	56 ± 14 (7.3 ± 1.3) [21]	–	–	53 ± 13 (7.0 ± 1.2)	–
AHI, events/h, median (range) [N_{alt}]	31 (5-116) [630]	33 (6-76)	NS	19 (5-30) [309]	18 (6-28)	NS	46 (30-116) [321]	50 (32-760)	NS
ODI, events/h, median (range) [N_{alt}]	20 (0-118) [630]	27 (1-99)	NS	11 (0-73) [309]	14 (1-45)	NS	35 (2-118) [321]	47 (6- 98)	NS
ESS, total score, mean ± SD [N_{alt}]	10.6 ± 5.0 [614]	9.9 ± 5.1 [50]	NS	10.5 ± 4.9 [305]	8.5 ± 5.2 [23]	< 0.05	10.8 ± 5.0 [309]	10.9 ± 4.4 [27]	NS
Snoring, n/N (%)	533/635 (84)	38/52 (73)	0.04	262/314 (83)	16/24 (67)	0.05	271/321 (84)	22/28 (79)	NS
Observed interrupted breathing, n/N (%)	430/633 (68)	35/51 (69)	NS	204/313 (65)	15/24 (63)	NS	226/320 (71)	20/27 (74)	NS
Nycturia, n/N (%)	454/617 (74)	46/53 (89)	< 0.05	220/302 (73)	21/24 (88)	NS	234/315 (74)	25/29 (87)	NS
Antihypertensive treatment, n/N (%)	224/635 (35)	44/54 (82)	< 0.001	99/313 (32)	19/24 (79)	< 0.001	125/322 (39)	25/30 (83)	< 0.001
Hypnotic drugs, n/N (%)	47/630 (8)	8/54 (15)	0.07	24/311 (8)	5/24 (20)	< 0.05	23/319 (7)	3/30 (10)	NS
Smoking, n/N (%)	166/624 (27)	5/53 (9)	< 0.01	89/306 (29)	3/24 (13)	0.08	77/318 (24)	2/29 (7)	< 0.05
Cardiovascular disease, n/N (%)	33/636 (5)	15/54 (28)	< 0.001	13/314 (4)	6/24 (25)	< 0.01	20/322 (6)	9/30 (30)	< 0.001
Cerebrovascular disease, n/N (%)	23/636 (4)	4/54 (7)	NS	11/314 (4)	2/24 (9)	NS	12/322 (4)	2/30 (7)	NS
Metformin, n/N (%)	–	40/54 (74)	–	–	18/24 (75)	–	–	22/30 (73)	–
Insulin, n/N (%)	–	13/54 (24)	–	–	9/24 (38)	–	–	4/30 (13)[b]	–
Sulfonylurea, n/N (%)	–	8/54 (15)	–	–	2/24 (8)	–	–	6/30 (20)	–
GLP-1 analogues, n/N (%)	–	7/54 (13)	–	–	3/24 (13)	–	–	4/30 (13)	–
Dipeptidylpeptidase-4 inhibitors, n/N (%)	–	4/54 (7)	–	–	0	–	–	4/30 (13)	–

AHI = Apnea Hypopnea Index; DM = diabetes mellitus; ESS = Epworth Sleepiness Scale; GLP = glucagon-like peptide; HbA_{1c} = glycated haemoglobin concentration; N_{alt} = alternative N-value; NS = non-significant; ODI = Oxygen Desaturation Index; SD = standard deviation; T2 = type 2.
a) p < 0.001 vs no DM (AHI: 5-30).
b) p = 0.04 vs DM (AHI: 5-30).

day-time sleepiness, snoring, observed interrupted respiration at night and comorbidities by. Finally, a clinical examination was performed before the patient was offered CPAP therapy.

Apnoea is a pause in breathing lasting at least ten seconds, while hypopnoea is defined as hypoventilation combined with oxygen desaturation > 4%. Apnea Hypopnea Index (AHI) is the average number of apnoeas and hypopnoeas per hour of sleep. The severity of OSA is commonly graded as mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30) or severe (AHI ≥ 30) [2, 3]. The Oxygen Desaturation Index (ODI) is the hourly average of episodes with desaturation > 4%. The last glycated Hb (HbA_{1c})-value before introducing CPAP therapy was obtained from laboratory records. The study was approved by The Danish Data Protection Agency and The Danish Health Authority.

Statistical analysis

Continuous variables are presented as mean ± standard deviation except for AHI and ODI (median and range), which were not normally distributed. Groups were compared by unpaired t-test or Mann Whitney test as appropriate. Categorical variables were analyzed by the chi-squared test or Fisher's test. $p < 0.05$ (two-sided) was considered statistically significant. The statistical programme used was SPSS ver. 20.0.

Trial registration: not relevant.

RESULTS

The database included 711 patients. We were unable to obtain a questionnaire or supplemental information in the records of 15 patients. Thus, the study is based on 696 patients, six with type 1 DM (0.9%) and 54 with type

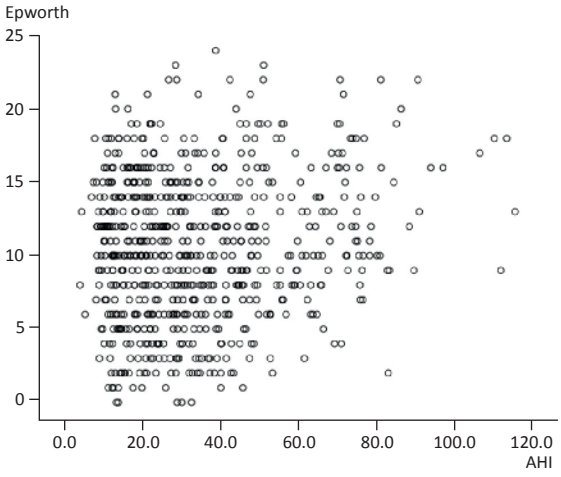
2 DM (7.8%). Compared with the non-diabetic group, the prevalence of antihypertensive treatment (82% versus 35%), cardiovascular disease (28% versus 5%), mean BMI (34.4 kg/m^2 versus 30.4 kg/m^2), mean age (60 years versus 53 years) and reported nycturia (89% versus 74%) was significantly higher patients with type 2 DM than in patients without (**Table 1**). The higher prevalence of cardiovascular disease in patients with diabetes was observed even when the analysis was restricted to patients ≥ 60 years (45% versus 10%, p < 0.001). In contrast, the prevalence of smokers was lower (9% versus 27%). A male preponderance (75%) was found in both groups. We found no difference in AHI, ESS or ODI between the groups.

Patients with mild and moderate OSA (AHI: 5-30) were analyzed as one group due to low numbers of patients with mild OSA. The group counted 338 patients, including 24 with type 2 DM (7.1%). A total of 352 patients had severe OSA (AHI ≥ 30); and among these, 30 had type 2 DM (8.5%). We found no significant association between the degree of OSA and the prevalence of diabetes. Patients with severe OSA, but without diabetes, were more often males and had higher BMI than those with mild-to-moderate OSA, while ESS was similar. The male preponderance persisted in type 2 DM with severe OSA, but no statistically significant difference was noted for age, BMI, ESS, OSA-related symptoms or HbA_{1c} compared with the diabetic group with mild-to-moderate OSA.

The majority of the type 2 DM group was referred from a general practitioner either directly (27%) or through an otorhinolaryngeal specialist (52%). Furthermore, 8% were referred from hospital departments specialized in neurological or pulmonary diseases or from other departments, whereas only 8% were referred from diabetes outpatient clinics. A total of 47 (76%) of the type 2 diabetes patients received medication for glycaemic control. Insulin was used more frequently for patients with mild-to-moderate OSA (38%) than for patients with severe OSA (10%, p < 0.05).

ESS in patients with mild-to-moderate OSA (5 < AHI < 30, n = 330) was 10.3 ± 5.0, which was not statistically different from ESS = 10.8 ± 5.0 for patients with severe OSA (AHI ≥ 30, n = 340); p = 0.2. Combined values for ESS and AHI are depicted in **Figure 1**.

FIGURE 1



Scatter plot of the Epworth Sleepiness Scale score and the Apnea Hypopnea Index (AHI) for 670 patients with newly diagnosed obstructive sleep apnoea.

DISCUSSION

We found a much lower prevalence of known type 2 DM (7.8%) in newly diagnosed OSA patients than expected from previous studies reporting OSA in between 12.5% and 30% patients with diabetes [11-16]. The prevalence of known type 2 diabetes in our study corresponds roughly to the prevalence (6.6%) in patients without OSA reported in the recent European Sleep Apnea Cohort (ESADA) study [15]. Our finding may, in part, depend on the fact that diabetes was self-reported and not based on a systematic screening as in the ESADA study, where the prevalence of type 2 diabetes was in 14% in mild and 29% in severe OSA. A study from Ireland reported an 8.8% prevalence of known type 2 diabetes in newly diagnosed OSA patients, which increased to 19% after measuring HbA_{1c} [16]. In another study including 494 men with OSA, 40% in the diabetes group were newly diagnosed after an oral glucose tolerance test [11]. In addition, in a Canadian study that included 1,717 OSA patients, the prevalence of reported type 2 DM increased from 9% (self-reported) to 12.5% after applying information from administrative databases [12]. Overall, the studies suggest that the true prevalence of type 2 diabetes in newly diagnosed OSA is nearly twice as high as the prevalence of known diabetes.

The prevalence of OSA in patients with type 2 DM has been reported in the range 23-86% [4-9] with the highest prevalence in obese (mean BMI = 36 kg/m^2) persons [9]. Obesity is associated with type 2 diabetes, which may explain why patients with both type 2 DM and OSA in this study were more overweight than persons with OSA but without diabetes. Referral bias cannot be ruled out, i.e. the possibility that diabetic persons needed to be more obese to be considered candidates for OSA screening. Furthermore, our results may be affected by preferential referral of persons without diabetes for OSA screening because this condition may still not be well recognized by the medical community in Denmark as a common diabetic comorbidity contrary to the well-known micro- and macrovascular complications. It is unknown if the prevalence of OSA in type 2 diabetes is higher than in non-diabetic persons of com-

Please be attentive to the coexistence of diabetes and obstructive sleep apnoea.

parable age and BMI. Our study suggests that the identification of patients with severe OSA cannot rely solely on symptoms since no significant difference between daytime sleepiness, snoring or observed interrupted breathing was noted between mild-to-moderate and severe OSA.

The severity of OSA is associated with poor glycaemic control (HbA_{1c}) in type 2 diabetes, even when adjusting for BMI and neck circumference, which might indicate an independent relation between the two conditions [15]. In our study, HbA_{1c} was similar in the group with mild-to-moderate OSA and in the group with severe OSA. This may be so because the majority was medicated and glycaemic control was close to a therapeutic target of 7% (53 mmol/mol). In contrast, the ESADA study reports diabetic medication in between 8% and 16% of type 2 diabetic patients depending on the severity of OSA [15]. In our study, 13% (with a mean BMI of 34 kg/m^2) received glucagon-like peptide-1 analogues. This treatment has been shown to reduce AHI and weight in persons with moderate-to-severe OSA declining CPAP [17], and to reduce daytime sleepiness in type 2 DM [18]. The effect on AHI remains to be elucidated. The higher frequency of insulin treatment in patients with low-to-moderate OSA is considered a random finding possible influenced by multiple tests for different medications.

The five-fold increase in the reported prevalence of cardiovascular disease in patients with type 2 DM with OSA signals the identification of a high-risk population. A study of 305 obese type 2 diabetic persons including 162 with mild to severe OSA reported a higher prevalence of cerebrovascular disease, but no coronary heart disease with increasing AHI [19]. Of note, we did not have a control diabetes group without OSA, and the suggestion that OSA is a cardiovascular risk factor adding to diabetes cannot be evaluated in the present study.

Daytime sleepiness is a cardinal symptom of OSA and is also regarded a risk factor for traffic accidents. However, we did not find subjective daytime sleepiness, assessed by ESS, to be associated with the severity of OSA.

The low prevalence of type 2 DM and the small fraction of patients referred from endocrinology outpatient clinics is an important finding underscoring the necessity of heightened attention to the association between diabetes and OSA from both the primary and the secondary healthcare sector. The patients were referred from all parts of the Central Denmark Region, and a similar referral pattern may be expected in the other four Danish regions. Our findings highlight the relevance of the recommendation of the IDF [10]. A systematic screening of newly diagnosed OSA patients for diabetes is advocated [16]. OSA is an orphan disease that does not naturally belong to a single medical field, but calls for a multidisciplinary approach including an endocrinological contribution.

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LITERATURE

1. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014;383:736-47.
2. Greenstone M, Hack M. Obstructive sleep apnoea. BMJ 2014;348:g3745.
3. Aurora RN, Punjabi NM. Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association. Lancet Respir Med 2013;1:329-38.
4. West SD, Nicoll DJ, Strading JR. Prevalence of obstructive sleep apnea in men with type 2 diabetes. Thorax 2006;61:945-50.
5. Einhorn D, Stewart DA, Erman MK et al. Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. Endocrine Pract 2007;13:355-63.
6. Laaban JP, Daenen S, Léger D et al. Prevalence and predictive factors of sleep apnoea syndrome in type 2 diabetic patients. Diabetes Metab 2009;35:372-7.
7. Schober A-K, Neurath MF, Harsch IA. Prevalence of sleep apnoea in diabetic patients. Clin Respir J 2011;5:165-72.
8. Storgaard H, Mortensen B, Almdal T et al. At least one in three people with type 2 diabetes mellitus referred to a diabetes centre has symptomatic obstructive sleep apnoea. Diabet Med 2014;31:1460-7.
9. Foster GD, Sanders MH, Millman R et al. Obstructive sleep apnea among obese patients with type 2 diabetes. Diab Care 2009;32:1017-9.
10. Shaw JE, Punjabi NM, Wilding JP et al. Sleep-disordered breathing and type 2 diabetes. A report from the International Diabetes Federation Taskforce on Epidemiology and Prevention. Diabetes Res Clin Pract 2008;81:2-12.
11. Meslier N, Gagnadoux F, Giraud P et al. Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome. Eur Respir J 2003;22:156-60.
12. Ronksley PE, Hemmelgarn BR, Heitman SJ. Obstructive sleep apnoea is associated with diabetes in sleepy subjects. Thorax 2009;64:834-9.
13. Mahmood K, Akhter N, Eldeirawi K et al. Prevalence of type 2 diabetes in patients with obstructive sleep apnea in a multi-ethnic sample. J Clin Sleep Med 2009;5:215-21.
14. Fusetti M, Fioretti AB, Valenti M et al. Cardiovascular and metabolic comorbidities in patients with obstructive sleep apnoea syndrome. Acta Otorhinolaryngol 2012;32:320-5.
15. Kent BD, Grote L, Ryan S et al. Diabetes mellitus prevalence and control in sleep-disordered breathing. The European Sleep Apnea Cohort (ESADA) Study. Chest 2014;146:982-90.
16. Fitzgerald DB, Kent BD, Garvey JF et al. Screening for diabetes mellitus in

patients with OSAS: a case for glycosylated haemoglobin. Eur Respir J 2012;40:273-4.
17. Blackman A, Foster G, Zammit G et al. Liraglutide 3.0 mg reduces severity of obstructive sleep apnoea and body weight in obese individuals with moderate or severe disease, SCALE sleep apnoea trial. (abstract). Diabetologia 2014;57(suppl 1):S85.
18. Gomez-Peralta F, Abrea C, Castro JC et al. An association between liraglutide treatment and reduction in excessive daytime sleepiness in obese subjects with type 2 diabetes. BMC Endocr Disord 2015;15:78.
19. Rice TB, Foster GD, Sanders MH et al. The relationship between obstructive sleep apnea and self-reported stroke or coronary heart disease in overweight and obese adults with type 2 diabetes mellitus. Sleep 2012;35:1293-8.