Obstructive sleep apnoea and retinopathy in patients with type 2 diabetes

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Online supplement
Obstructive Sleep Apnea and Diabetic retinopathy in Patients with Type 2 Diabetes: A Longitudinal Study

OSA severity and DR

In order to assess the relationship between OSA severity and STDR, we used the logistic regression model shown in Table 4. Inserting OSA as a three category variable (no OSA, mild and moderate to severe OSA) demonstrated that mild (OR 2.7, 95%CI 1.2-6.1, p=0.01) but not moderate to severe (OR 1.9, 95%CI 0.7-4.8, p=0.1) OSA was independently associated with STDR. A similar association was found with maculopathy (mild OSA- OR 3.1, 95%CI 1.3-7.1, p=0.006; and moderate to severe OSA- OR 2.3, 95%CI 0.9-6.1, p=0.08) and advanced DR (mild OSA- OR 3.0, 95%CI 0.9-9.9, p=0.06; and moderate to severe OSA- OR 3.1, 95%CI 0.8-12.3, p=0.09).

To assess the relationship between OSA and ODI and STDR as well as maculopathy and advanced DR we used AHI and ODI tertiles instead of OSA in the same model detailed in Table 4. The AHI tertiles were: tertile 1 AHI < 4.8 events/hour, tertile 2 AHI 4.8-11.89 events/hour and tertile 3 ≥ 11.90 events/hour. The ODI tertiles were tertile 1 ODI < 4.1 events/hour, tertile 2 ODI 4.1-11.39 events/hour and tertile 3 ODI ≥ 11.40 events/hour.

After adjusting for ethnicity, age at diabetes diagnosis, diabetes duration, gender, HbA1c, BMI, systolic blood pressure, insulin use, number of anti-hypertensive agents, oral anti-hyperglycaemic agents and eGFR there was a non-significant trend of association between AHI tertiles and STDR (Nagelkerke R^2 for the model= 0.32); the OR (95%CI) for AHI tertiles 2 and 3 considering tertile 1 as the reference point were OR 1.9 (95% CI 0.8-4.4, p=0.1) and OR 2.1 (95%CI 0.9-5.0, p=0.1) respectively. Replacing AHI tertiles with ODI tertiles showed that the association with tertile 2 was

statistically significant. After similar adjustments (Nagelkerke R^2 for the model= 0.33); the OR (95%CI) for ODI tertiles 2 and 3 considering tertile 1 as the reference point were OR 2.6 (95%CI 1.2-5.9, p=0.02) and OR 1.8 (95%CI 0.7-4.3, p=0.2) respectively.

Repeating the same analysis but replacing the outcome measure from STDR to maculopathy showed that tertiles 2 of the AHI and ODI were significantly associated with maculopathy at baseline with a non-significant trend of association with tertiles 3 of the AHI and ODI. The OR (95%CI) for tertiles 2 and 3 of AHI were (Nagelkerke R^2 for the model 0.27) OR 2.5 (95%CI 1.1-5.7, p=0.03) and OR 2.2 (95%CI 0.9-5.4, p=0.09) respectively. The OR (95%CI) for tertiles 2 and 3 of ODI were (Nagelkerke R^2 for the model 0.27) OR 2.5 (95%CI 1.1-5.6, p=0.03) and OR 1.8 (95%CI 0.7-4.4, p=0.2) respectively.

Repeating the analysis but changing the outcome measure to advance DR showed a non-significant association between advanced DR and tertiles 2 and 3 of AHI and ODI. For AHI tertiles 2 and 3 (Nagelkerke R^2 for the model 0.31) the OR (95%CI) were OR 2.7 (95%CI 0.8-9.0, p=0.1) and OR 2.8 (95%CI 0.8-10.3, p=0.1) respectively. For ODI tertiles 2 and 3 (Nagelkerke R^2 for the model 0.32) the OR (95%CI) were OR 3.2 (95%CI 1.0-10.4, p=0.05) and OR 2.5 (95%CI 0.7-8.9, p=0.2) respectively.

Characteristics of the study population that was examined for the progression to advanced DR

164 patients included in this analysis of which 66 (40.2%), 60 (36.6%), 19 (11.6%) and 19 (11.6%) had no, mild, moderate and severe OSA respectively. All patients with moderate to severe OSA (n=38) were referred to the sleep clinic in the NHS trust and that's why we had 38 patients in the CPAP table in the online supplement. The baseline characteristics of the 164 patients who were included in the progression to advanced DR analysis are summarised in Table 1 of the online supplement. The characteristics of this population are in line with the characteristics of the total population at baseline (Table 2 of the main manuscript)

Table 1 of the online supplement: The baseline characteristics of the 164 patients who were included in the progression to advanced DR analysis. Data presented as mean (SD) or % (n). Analysis performed using the Chi-square test for categorical variables, the independent t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

	OSA- (n=66)	OSA+ (n=98)	P value
Male	40.9% (27)	66.3% (65)	0.001
White European	31.8% (21)	56.1% (55)	0.002
Age (years)	54.9 (11.3)	58.8 (11.9)	0.02
Diabetes duration (years)	10.9 (7.3)	12.1 (7.2)	0.18
Body Mass Index (kg/m^2)	31.6 (7.3)	36.0 (10.0)	0.001
Waist circumference (cm)	105.7 (13.7)	115.6 (16.9)	< 0.001
Systolic blood pressure (mmHg)	124.1 (15.6)	132.2 (13.9)	0.001
Diastolic blood pressure (mmHg)	76.9 (10.5)	78.3 (9.6)	0.63
HbA1c (%)	7.8 (1.3)	8.2 (1.3)	0.02
Total cholesterol (mmol/L)	4.0 (1.1)	3.8 (0.9)	0.20
Triglycerides (mmol/L)	1.9 (1.3)	2.0 (1.2)	0.30
Estimated GFR (ml/min/1.73 m^2)	93.1 (23.2)	85.4 (26.5)	0.03
Epworth sleepiness score	6.2 (5.9)	8.9 (5.8)	0.003
Smoking (current or ex-smoker)	37.9% (25)	38.8% (38)	0.91
Alcohol (consumes alcohol)	10.6% (7)	23.5% (23)	0.04
Oral hypoglycaemic agents	98.5% (65)	88.8% (87)	0.03
Thiazolidinediones	15.2% (10)	12.2% (12)	0.59
Insulin	37.9% (25)	55.1% (54)	0.03
GLP-1 analogue	4.5% (3)	11.2% (11)	0.13
Anti-hypertensive agents	72.7% (48)	83.7% (82)	0.09
Lipid lowering therapy	89.4% (59)	84.7% (83)	0.39
Fibrates	6.1% (4)	4.4% (4)	0.72
Anti-platelet agents	62.1% (41)	71.4% (70)	0.21
Ischemic heart disease	15.2% (10)	23.5% (23)	0.19
Diabetic nephropathy	20.3% (13)	47.9% (45)	< 0.001

The impact of HbA1c changes during the follow-up on the relationship between OSA and progression to advanced DR

As hyperglycaemia is a major risk factor for the development of DR, we wanted to explore whether changes in HbA1c from baseline are responsible for the associations observed between OSA and progression to advanced DR. The follow up HbA1c was collected mostly in 2013 and 2014 using the latest HbA1c available in the electronic patients records. The median (IQR) follow up duration for HbA1c in patients in whom we made the assessment for progression to advanced DR was 3.8 (3.3-4.4) years vs. 4.0 (3.4-4.5) years for patients without vs. with OSA (p=0.2). The longitudinal changes in HbA1c based on OSA status at baseline in patients in which we made the advanced DR progression assessment are summarised in Table 2 of the online supplement. HbA1c change was calculated as study-end HbA1c – baseline HbA1c (i.e. positive numbers indicate worsening HbA1c).

Table 2 of the online supplement: Changes in HbA1c and their relationship to OSA status during the study follow-up. Data presented as mean (SD) or median (IQR). *indicate p value for the difference between patients with and without OSA; $^{\$}$indicate p value for the difference between baseline and study end in the same OSA status category. The sample size analysis is 164 at baseline and 163 patients at study-end as there is one HbA1c measurement missing from a patient with OSA at baseline.

	Baseline HbA1c	Study-end HbA1c	P value$^{\$}$	HbA1c change
No OSA (n=66)	7.8 (1.3) %	8.1 (1.6) %	0.03	0.1 (-0.3 to 0.8)
OSA (n=97)	8.2 (1.3) %	8.1 (1.8) %	0.6	0.0 (-0.8 to 0.7)
P value*	0.02	0.9		0.07

The results show that in the no OSA group HbA1c has worsened over the follow up period while it remained stable in patients with OSA. However, despite the worsening of HbA1c in patients without OSA, OSA was associated with the progression to advanced DR.

Adding change in HbA1c in the logistic regression model showed that OSA remained associated with the development of progression to advanced DR (Nagelkerke R^2 0.42; OR 5.3; 95%CI 1.2-23.5, p=0.03). Similarly, adjusting for study-end HbA1c instead of HbA1c change did not affect the results and OSA remained associated with progression to advanced DR (Nagelkerke R^2 0.42; OR 5.3, 95%CI 1.2-23.5, p=0.03).

Hence, in summary, HbA1c change during the follow up did not explain the observed relationship between OSA and progression to advanced DR.

CPAP and DR progression

Out of 164 patients that were included in the progression to advanced DR analysis, 38 had moderate to severe OSA and only 15 were CPAP-compliant. Summary of patient characteristics according to CPAP compliance can be found in Table3 of the online supplement. There were largely no differences between patients who were and were not compliant with CPAP; apart from that the AHI was higher in the CPAP compliant group and use of diabetes treatment (both oral anti-diabetic drugs and insulin) was higher in CPAP non-compliant group.

Progression to advanced DR occurred in 6% (n=4) vs. 15.3% (n=9) vs.39.1% (n=9) vs. 0% (n=0) in patients with no OSA, mild OSA, moderate to severe OSA non-compliant with CPAP and moderate to severe OSA compliant with CPAP respectively (p<0.001).

Out of 129 patients included in the progression to maculopathy analysis, 28 patients had moderate to severe OSA, of which 11 were CPAP-compliant. Progression to maculopathy occurred in 19.0% (n=11), 18.6% (n=8), 35.3% (n=6) and 9.1% (n=1) in patients with no OSA, mild OSA, moderate to

severe OSA non-compliant with CPAP and moderate to severe OSA compliant with CPAP respectively (p=0.34). Similar trends were found in the progression to sight threatening DR analysis but results were not statistically significant.

Table 3 of the online supplement: Comparison of the characteristics of patients who were and were not compliant with CPAP treatment. Data presented as mean (SD) or n (%) of the respective CPAP group.

	CPAP non -compliant (n=23)	CPAP compliant (n=15)	P value
Male	19 (82.6%)	9 (60.0%)	0.002
White Europeans	15 (65.2%)	11 (73.3%)	0.003
Age (years)	61.3 (9.5)	61.9 (7.0)	0.82
Diabetes Duration (years)	13.0 (6.7)	12.0 (8.0)	0.94
Body Mass Index (kg/m^2)	36.3 (9.0)	39.4 (10.1)	0.34
Waist circumference (cm)	118.3 (14.9)	119.4 (19.3)	0.85
Systolic blood pressure (mmHg)	131.4 (15.2)	135.6 (14.4)	0.40
HbA1c (%)	8.0 (1.5)	7.7 (1.0)	0.42
Total cholesterol (mmol/L)	3.6 (0.7)	4.0 (1.2)	0.20
Triglycerides (mmol/L)	2.2 (0.9)	1.5 (0.8)	0.01
AHI (events/hour)	31.1 (18.7)	43.7 (25.1)	0.08
Epworth sleepiness score	9.9 (6.0)	10.6 (4.7)	0.7
Oral anti-diabetes treatment	22 (95.7%)	12 (80.0%)	0.03
Insulin	13 (56.5%)	6 (40.0%)	0.07
Anti-hypertensive agents	20 (87.0%)	14 (93.3%)	0.2
Lipid lowering treatment	20 (87.0%)	15 (100.0%)	0.1
Anti-platelets	18 (78.3%)	11 (73.3%)	0.5

Figure 1 of the online supplement: The follow up duration in patients with no DR at baseline (R0) according to study-end DR grade in patients with and without OSA. DR: diabetic retinopathy. There was no progression from R0 to R2.