REVIEW

Diabetes Management

Obstructive sleep apnea in patients with diabetes: implications for clinical practice

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Practice points

- Obstructive sleep apnea is very common in patients with Type 2 diabetes.
- Obstructive sleep apnea is a risk factor for incident Type 2 diabetes independent of obesity.
- Obstructive sleep apnea is associated with hypertension and treatment with continuous positive airway pressure lowers blood pressure.
- Obstructive sleep apnea is associated with cardiovascular disease and increased mortality.
- Obstructive sleep apnea is associated with worse glycemic control independent of obesity in patients with Type 2 diabetes but the impact of continuous positive airway pressure treatment is unclear.
- Obstructive sleep apnea is associated with vascular complications in patients with Type 2 diabetes and might contribute to the progression of these complications; the impact of continuous positive airway pressure treatment is being examined.
- Obstructive sleep apnea has a wide range of symptoms that are common in patients with Type 2 diabetes such as snoring, headache, tiredness, sweating, erectile dysfunction.
- A high index of suspicion is required to diagnose obstructive sleep apnea in patients with Type 2 diabetes.

Obstructive sleep apnea (OSA) is very common in patients with Type 2 diabetes (T2D). Over the last two decades there has been increasing interest in the impact of OSA on glucose metabolism and the impact of OSA in patients with T2D, which mostly focused on the impact of OSA on glycemic measures. However, more recently the impact of OSA on diabetes-related vascular risk factors and outcomes in patients with T2D gained interest. In this article I will briefly review of the epidemiology and impact of OSA in patients with T2D with particular focus on the impact of OSA on diabetes-related outcomes such as hyperglycemia, cardiovascular disease risk factors and vascular complications.

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Over the last two decades there has been an increasing interest in the impact of obstructive sleep apnea (OSA) on glucose metabolism. Considering that obesity is a common risk factor, it is not surprising that OSA and Type 2 diabetes (T2D) commonly co-exist. While several epidemiological studies and clinical trials showed that OSA is associated with insulin resistance and increased risk of T2D hypertension, cardiovascular disease (CVD), mortality and road traffic accidents, the impact of OSA in patients with T2D has only been studied more recently [1].

In this article I will provide a brief review of the epidemiology and impact of OSA in patients with T2D with particular focus on the impact of OSA on diabetes-related outcomes such as hyperglycemia, CVD risk factors and vascular complications. I will also review the current evidence for OSA treatment in patient with T2D. The article will mainly focus on evidence from clinical studies.

Obstructive sleep apnea

• Overview

OSA is a common disorder that affects 17–26% in men and 9–28% in women [2]. OSA is characterized by upper airway instability during sleep, which results in recurrent upper airway obstruction resulting in either complete or partial cessation of airflow (i.e., apnea and hypopnea, respectively) [3]. The recurrent obstructions of the upper airway usually result in recurrent oxygen desaturations/resaturations, cyclical changes in intrathoracic pressure (as the patient attempts to breath against a blocked airway) and recurrent micro arousals that cause sleep fragmentation and reduction in slow wave and rapid eye movement (REM) sleep and result in termination of the apnea/hypopnea episode [3]. Apneas are defined as cessation or ≥90% reduction in airflow for a period of ≥10 s, while hypopneas have multiple definitions; a commonly used definition is ≥30% reduction in airflow for ≥10 s associated with ≥4% drop in oxygen saturations [4]. An apnea–hypopnea Index (AHI), which is the average number apnea and hypopnea episodes per hour during sleep, ≥5 events/hour is consistent with the diagnosis of OSA [3,5]. AHI cut offs of 15 and 30 are used to define moderate and severe OSA [6].

• Risk factors

Obesity is the most important risk factor of OSA, but not all patients with OSA are obese [7]. A BMI increase by 1 standard deviation (SD) was associated with a fourfold increase in OSA prevalence in the Wisconsin Sleep Cohort Study [8]. Prospective studies showed that weight gain resulted in an increased risk of incident OSA and worsening pre-existing OSA in those with and without OSA, respectively [9,10]. Relative to patients with stable weight, a 10% weight gain was associated with 32% (95% CI: 20–45%) increase in the AHI and increased risk of developing moderate-to-severe OSA (OR: 6.0; 95% CI: 2.2–17.0) [9]. Similarly, a 10% weight loss was associated with a 26% (95% CI: 18–34%) reduction in AHI [9]. Furthermore, randomized controlled trials showed that weight loss (vial life style modifications or surgical intervention) results in significant improvements or remission of OSA [11,12]. Obesity can contribute to the development of OSA via multiple mechanisms. Obesity can increase parapharyngeal fat deposition resulting in a smaller and more collapsible upper airway. Obesity can also alter the neural compensatory mechanisms that maintain airway patency, reduce the functional residual capacity with a resultant decrease in the stabilizing caudal traction on the upper airway and affect the chemosensitivity to O_2 and CO_2 which reduces ventilator drive [13].

In addition to obesity, OSA has many other risk factors including male gender, ethnicity, current smoking, excess alcohol intake and genetic factors [2,7,14–19].

• Symptoms

Snoring is the most common symptom of OSA and it occurs in 95% of patients [3] with only 6% of OSA patients have no history of self (or partner) reported snoring [3]. Witnessed apneas are also common but can be reported in up to 6% of patients without OSA [3]. Excessive daytime sleepiness (EDS) is associated with OSA but in general population other factors such as depression and the metabolic syndrome seem to be associated with EDS more than OSA [3,20–21]. Other symptoms such as choking, insomnia, nocturia, sweating, fatigue, morning headache, erectile dysfunction and autonomic symptoms have also been reported [3,22]. It must be noted that many of these symptoms are common in patients with T2D and might be as a result of diabetes-related complications such hypoglycemia, hyperglycemia or autonomic dysfunction and hence OSA should be considered in such patients after ruling out the diabetes-related factors.

• Comorbidities

OSA is associated with several comorbidities. OSA was associated with road traffic accidents in cross-sectional studies and predicted the occurrence of road traffic accidents in longitudinal studies [2,23–24]. The use of continuous positive airway pressure (CPAP) ≥4 h/night resulted in reduction of the risk of road traffic accidents [25]. OSA was also associated with hypertension and lack of nocturnal dipping of blood pressure (BP) in longitudinal studies [9,26–27]; interventional studies showed that CPAP can lower diurnal and nocturnal BP [28–30]. Longitudinal studies also showed that patients with OSA were at increased risk of cardiovascular disease, which was reduced in those treated with CPAP [31–33], and more likely to develop acute myocardial infarction between 12 am and 6 am compared with matched patients without OSA (32 vs 7%; p = 0.01) supporting the role of the nocturnal events that occur in OSA patients in the development of CVD [34]. Similarly, prospective studies showed that OSA was associated with increased risk of mortality [35,36].

• OSA & dysglycaemia

The relationship between OSA and insulin resistance (IR) attracted much interest in the literature. Most cross-sectional studies [37–57], but not all [58–64], showed an association between OSA and IR. The studies that did not show an association had smaller sample size and were potentially underpowered [1]. The association between OSA and IR seems stronger in those with EDS compared with those without [65,66]. Obesity is obviously a major confounder for the relationship between OSA and IR but several studies in lean men with OSA or in patients in which OSA was driven by diseases other than obesity (such as acromegaly) also showed an association between OSA and IR [67–69], which suggest that the relationship between OSA and IR is independent of obesity [70].

The impact of OSA on IR was examined in a longitudinal study which showed that over 11-year follow-up OSA, AHI, oxygen desaturation index (ODI) and minimal oxygen saturations were independently associated with worsening IR (defined as exceeding the 75th percentile of the change in Homeostasis Model Assessment-insulin resistance [HOMA-IR]) after adjustment for age, baseline BMI, hypertension, BMI change over follow-up and CPAP treatment [71]. Several meta-analysis showed that CPAP lowers insulin resistance [72–74], particularly in those compliant with treatment and using CPAP >4 h/night [75].

β-cells failure plays a major role in the development and progression of T2D. When the β-cells fail to produce enough insulin to overcome insulin resistance, impaired glycemic tolerance and T2D ensues. The progressive nature of β-cells dysfunction contributes to the need for escalating the glucose lowering treatments in patients with T2D overtime. The impact of OSA on β-cells has scarcely been examined. One study in humans showed that OSA was associated with β-cell dysfunction in patients without T2D [76]. Prospective and interventional studies assessing the impact of OSA and its treatment on insulin resistance and β-cell function are needed.

Due to its impact on IR and possibly β-cell function it is not surprising that prospective longitudinal studies showed an increased risk of T2D (based on physician diagnosis, fasting plasma glucose or oral glucose tolerance test [OGTT]) in patients with OSA independent of age, obesity and other possible confounders [71,77–82]. A meta-analysis of published studies that used objective measures to diagnose OSA found that moderate to severe OSA was associated with increased risk of developing T2D (moderate-to-severe OSA: RR: 1.63; 95% CI: 1.09–2.45; mild OSA: RR: 1.22; 95% CI: 0.91–1.63) [83].

There are several biologically plausible mechanisms that might contribute to the links between OSA, IR and the risk of T2D [6,70,84–85]. The intermittent hypoxia and the repetitive episodes of reoxygenation result in increased oxidative and nitrosative stress, increased HIF-1, activation of the hypothalamic pituitary adrenal axis, increased catecholamines and reduction in adiponectin levels [2,84–91,1]. OSA is also associated with increased sympathetic activity, increased inflammation particularly increased IL-6, TNF-α and NF-κB and increased risk for the developing of histologically proven nonalcoholic fatty liver disease and for progressing to nonalcoholic steatohepatitis [55,92–93]. All of these factors might contribute to the association between OSA, IR and incident T2D.

Whether CPAP treatment improves glycemic measures in patients with prediabetes remains unclear but one recent RCT showed that 8 h of CPAP treatment reduced the area under the

curve for the 2-h overall glucose response during OGTT compared with placebo and resulted in improvements in insulin sensitivity, 24-h blood pressure and norepinephrine levels [94]. However, this study was relatively small (n = 39), of short duration (2 weeks) and was conducted in laboratory environment to ensure high compliance with CPAP under direct supervision which might prove difficult to achieve in real life. However, this study was designed to test the hypothesis that longer CPAP treatment might have better impact on glucose levels as the association between OSA and HbA1c seems stronger for the apnea–hypopnea events occurring during REM rather than non-REM sleep [95]. Further studies are needed to determine whether CPAP can lower the risk of incident diabetes in this group of patients.

OSA in patients with T2D

• Epidemiology

As we discussed previously in this article, obesity is a shared common risk factor between OSA and T2D; and considering that OSA is a risk factor for incident T2D it is predictable that several studies have shown a high prevalence of OSA in patients with T2D (8.5–85% with 23.8–70% for moderate-to-severe OSA) **(Table 1)** [96–108]. The differences between these studies are likely to reflect the differences in the population examined and differences in the methods and definitions used to diagnose OSA **(Table 1)**. The International Diabetes Federation (IDF) recommended screening for OSA in patients with T2D [109].

However, whether this high prevalence of OSA in patients with T2D is more than expected from similarly obese population without T2D is unclear. A recent cross-sectional analysis of the European Sleep Apnea Cohort (ESADA; n = 6616) suggested that T2D prevalence increased with worsening OSA (6.6 vs 28.9% for patients without OSA vs severe OSA, respectively). After adjustment for obesity and other confounding factors, mild, moderate or severe OSA had an OR (95% CI) of 1.33 (1.04–1.72), 1.73 (1.33–2.25) and 1.87 (1.45–2.42; $p < 0.001$), respectively, for prevalent T2D in comparison with subjects free of OSA [110].

• OSA & insulin resistance, β-cell & glycemic control

Data about the impact of OSA about IR and β-cell dysfunction in patients with T2D are rather limited. Two cross-sectional studies from the same group showed that OSA was associated with IR (based on HOMA) in patients with T2D [111,112]. A recent meta-analysis [113] of two nonrandomized trials [114,115] showed that CPAP treatment improved insulin sensitivity in patients with T2D. In regards to β-cell function one study in women with T2D showed that OSA was associated with β-cell dysfunction [112]. Longitudinal studies and RCTs assessing the impact of OSA and its treatment on IR and β-cell function in patients with T2D are needed.

Several cross-sectional studies (mostly small with n = 31–92 except ESADA with n = 6616) showed that OSA is associated with poorer glycemic control (HbA1c or fasting plasma glucose or glycemic variability) despite adjustments for a wide range of confounders including age, sex, race, BMI, number of diabetes medications, level of exercise, diabetes duration and total sleep time in some studies [105,110,116–119]. The impact of OSA on HbA1c varied considerably between studies with a HbA1c difference between patients with and without OSA of 0.7–3.69% in part due to differences in OSA severity. However, some studies also did not show an association between OSA and HbA1c [100,120]. These conflicting results might be due to several reasons including differences in the population characteristics or the methodology used to diagnose OSA. In the study by Einhorn *et al.* [100] only 22% of participants had full polysomnography and the duration of the sleep study was just 4 h [121]. Tamura *et al.* found that the lowest nocturnal arterial oxyhaemoglobin saturation correlated negatively with HbA1c (i.e., lower nocturnal oxygen saturations were associated with higher HbA1c values) [120]. Another factor that might explain the conflicting results between studies is the different distribution of AHI across REM and non-REM sleep as the association between the AHI and HbA1c seems to be limited to the apnea–hypopnea events that occurred during REM rather than non-REM sleep [95].

The impact of CPAP treatment on glycemic measures in patients with T2D was assessed in several studies **(Table 2)** [96,122–129]. Only one of these studies was a RCT [122] and the rest were uncontrolled studies. The uncontrolled studies showed improvements in insulin sensitivity [96,123], postprandial hyperglycemia [124], glycemic variability [127] and/or HbA1c [124,125].

Table 1. Summary of studies that examined obstructive sleep apnea prevalence in patients with Type 2 diabetes.

Study (year)	Population	Samples size	OSA diagnosis	OSA prevalence	Notes	Ref.
Brooks (1994)	Australia BMI >35	31	Ambulatory sleep monitoring	70% moderate to severe OSA	Sample was selected from a larger population based on OSA symptoms	[96]
Elmasry (2001)	Hepertensive men, 21% had diabetes, age 61.4 years (8.0), BMI 29.3 (4.5)	116	PSG OSA defined as AHI ≥20	36% in the diabetes group	The sample that had PSG was chosen based on questionnaires	[97]
Resnick *et al.* (2003)	A subgroup from the Sleep Health Heart study	470	PSG OSA defined as RDI ≥5 Moderate-to-severe RDI ≥15	OSA prevalence 57.8% Moderate-to-severe 23.8%	Self reported diabetes diagnosis or use of medications	[98]
West (2006)	All men, mixed primary and secondary care populations, UK, age 61.2 years (9.7), BMI 29.6 (5.4)	1676	Oximetry OSA defined as ODI >10	23%	Population screened by questionnaires. A subgroup was selected for oximetry	[99]
Einhorn (2007)	Consecutive adults with Type 2 diabetes from a diabetes clinic in the USA	330	Single-channel device that measured nasal airflow OSA defined as AHI ≥10	48% In moderate-to-severe OSA: 36%		[100]
Laaban *et al.* (2009)	Consecutive hospitalized patients with poorly controlled Type 2 diabetes mellitus	303	Overnight ventilatory polygraphic study. OSA defined as RDI ≥5 Moderate to severe RDI ≥15	OSA: 63% Moderate-to-severe: 29%		[101]
Foster (2009)	Community-based population from the USA (19.1% Afro–Caribbean), age 61 years. 3 years (6.5), BMI 36.5 (5.8)	306	PSG OSA defined as AHI ≥5 moderate/severe OSA: AHI ≥15/30	86% 30.5% for moderate OSA, 22.6% for severe OSA	Only overweight or obese individuals were included	[102]
Lam (2010)	Randomly selected patients from a teaching hospital diabetes clinic in China, age 57.3 years (9.3), BMI 26.0 (4.6)	165	PSG OSA defined as AHI ≥5 moderate/severe OSA: AHI ≥15	53.9% had OSA 32.7% had moderate to severe OSA	Patients with RRT were excluded	[103]
Schober (2011)	Secondary care sample from Germany	498	Multichannel respiratory device OSA defined as AHI ≥15	37.4%	This study also included patients with Type 1 diabetes, OSA prevalence 10.3%	[104]
Pillai (2011)	Consecutive patients from secondary care diabetes obesity clinic in the UK	52	PSG	58%	Participants had risk factors for OSA	[105]
Tahrani (2012)	Randomly selected patients from secondary care in the UK, 45% are South Asians. Age 57 years (12), BMI 34.4 (30.9–39.5)	234	Multichannel cardio-respiratory device OSA defined as AHI ≥5	65% Moderate-to-severe OSA: 26%	Patients with RRT were excluded. Prevalence was not the primary outcome of the study	[106]
Heffner (2012)	Case notes study from primary care in the USA, age 64 years (14.1), BMI 33.7 (8.3)	16,066	Physician diagnosis	18% of known OSA 23% had OSA among obese patients	This study did not screen for OSA, it simply reports the prevalence of known OSA, hence the lower prevalence than other studies	[107]

AHI: Apnea–hypopnea Index; OSA: Obstructive sleep apnea; PSG: Polysomnography; RDI: Respiratory disturbance Index; RRT: Renal replacement therapy.
Adapted with permission from [6].

Table 2. Summary of studies that examined the impact of continuous positive airway pressure treatment on glycemic control in patients with Type 2 diabetes.

Study (year)	Population	Study design	Control group	Matching or confounder adjustment	Outcome measure	Duration	CPAP usage	Effectiveness	Ref.
Brooks (1994)	n = 10 Australia Obese T2D (BMI >35)	Pre and post	No	No	Glucose disposal during hyperinsulinemic euglycemic clamp	4 months	NR	+	[96]
Harsch (2004)	n = 9 Severe OSA BMI 37.3 (5.6) HbA1c 6.4 (0.7)%	Pre and post	No	No	ISI established by euglycemic hyperinsulinaemic clamp	3 months	5.8 h/night	-	[123]
Babu (2005)	n = 25 Severe OSA BMI 42.7 (8.7), HbA1c 8.3 (2.2) Diabetes duration 8.6 years (6.3)	Pre and post	No	No	72 h CGMS and HbA1c	3 months	4.2 h/night	+	[124]
Hassaballa (2005)	n = 38 Severe OSA BMI 42 (9.5) HbA1c 7.8 (1.4)%	Pre and post	No	No	HbA1c	4 months	4 h/night	+	[125]
West (2007)	n = 42 Age 57.8 years (10.4), BMI 36.6 (4.9), HbA1c 8.5 (1.8)	RCT	Yes	N/A	HbA1c	3 months	3.6 h/night	-	[122]
Dawson (2008)	n = 20 Moderate-to-severe OSA, age 59.8 years (10.2), BMI 39.6 (8.0), diabetes duration 9.8 (7.7) HbA1c 7.2%	Pre and post	No	No	CGMS HbA1c	41 days	5.8 h/night	+ for glucose variability - for HbA1c	[126]
Pallayova (2008)	n = 14 Severe OSA Age 54 years (6), BMI 37.4 (6.3) Diabetes duration 3.7 (1.5), HbA1c 7.48 (0.92)%	Pre and post	No	No	CGMS	NR	NR	+	[127]

CGMS: Continuous glucose monitoring system; CPAP: Continuous positive airway pressure; ISI: Insulin Sensitivity Index; NR: Not reported; OSA: Obstructive sleep apnea.
Adapted with permission from [6].

The RCT showed no change in HbA1c after 3 months of CPAP therapy [122], this could be because of true lack of effect, the sample size, the relatively short duration of treatment or the lack of CPAP compliance (3.6 h/night). Several meta-analysis showed that CPAP did not significantly reduce HbA1c in patients with T2D [73,113,130].

As discussed above, the association between OSA and HbA1c seems stronger for the apnea–hypopnea events occurring during REM rather than non-REM sleep [95]. This might suggest that CPAP treatment during REM might have a bigger impact on glycemic measures and as REM occur predominantly toward the end of the night then a prolonged CPAP use (beyond the usual cut off of 4 h per night) would be required to have an impact on HbA1c. This might explain the lack of impact of CPAP in the RCT by West *et al.*; however, whether prolonged use of CPAP with high compliance is achievable in real life and outside laboratory settings remains to be seen. Further well-designed, adequately powered RCTs with adequate treatment duration and compliance are needed to answer the question whether OSA treatment can improve glycemic control in patients with T2D [131].

• OSA & hypertension

Unlike the well-established link between OSA and hypertension in general population studies, the evidence in patients with T2D is rather limited. In a retrospective cohort study, 9–12 months of CPAP was associated with a mean (95% CI) change of -6.81 mmHg (-9.94 to -3.67 mmHg) and -3.69 mmHg, (-5.53 to -1.85 mmHg) in systolic and diastolic BP, respectively, in patients with T2D [132]. Similar results were found after 3 months of CPAP in a randomized parallel group intervention trial in which patients with T2D were randomized to early (<1 week) versus late (1–2 months) CPAP [129]. Well-designed longitudinal studies and randomized placebo and active controlled trials are needed to understand the impact of OSA and its treatment on BP in patients with T2D assessing particularly in those with resistant hypertension.

• OSA & vascular complications

The impact of OSA on diabetes-related vascular outcomes is an emerging field of research. In the Look AHEAD study AHI was associated with self-reported history of stroke (adjusted OR: 2.57, 95% CI: 1.03–6.42), but not with coronary artery disease in a cross-sectional analysis [133]. A more recent study provided robust evidence of an association between OSA and CVD. In this study 132 consecutive asymptomatic patients with T2D and normal exercise echocardiography for ≤8 years were followed for a median of 4.9 years and found that OSA was associated with incident coronary artery disease (adjusted HR: 2.2; 95% CI: 1.2–3.9; p = 0.01) and heart failure (adjusted HR: 3.5; 95% CI: 1.4–9.0; p < 0.01) over the follow-up period [134]. Whether CPAP treatment reduces CVD progression or incidence in patients with T2D is unknown.

Similarly the evidence linking OSA to microvascular complications in patients with T2D is limited as all but one of the studies is cross-sectional. In Japanese patients undergoing vitreous surgery for advanced diabetic retinopathy (DR), lower oxygen saturations were associated with proliferative DR after adjustment for age, HbA1c and hypertension [135]. In a study from the UK, OSA was independently associated with DR and maculopathy after adjusting for age, BMI, diabetes duration and hypertension in men with T2D [136]. Similarly, in another study from the UK, patients with OSA were three- to four-times more likely to have sight threatening DR, preproliferative/proliferative DR or maculopathy after adjustment for a wide range of confounders including gender and ethnicity [137]. Longitudinally, patients with OSA were more likely to develop preproliferative/proliferative DR (adjusted OR: 6.6; 95% CI: 1.2–35.1; p = 0.03); and patients who were compliant with CPAP treatment had lower progression to preproliferative/proliferative DR compared with noncomplaint patients [137]. In an uncontrolled, hypothesis generating study, CPAP treatment for 6 months was associated with improvement in visual acuity without an impact on macular oedema/thickness suggesting improved functionality rather actual change in the oedema [138]. Similar to the associations with DR, OSA was found to be associated with diabetic nephropathy (defined as albuminuria and/or reduced eGFR) in patients with T2D (adjusted OR: 2.64; 95% CI: 1.13–6.16; p = 0.02) [139]. After a 2.5-year follow-up, the eGFR decline was greater in patients with OSA compared with those without OSA (median: -1.4% [IQR: -7.7–5.2] vs -5.3% [-16.5–2.7] vs -8.7% [-16.1–2.0]; p = 0.003, for no OSA vs mild vs moderate-to-severe OSA) and OSA was an independent predictor of study-end eGFR (B =

-4.2; p = 0.03) and eGFR decline [139]. In the same observational longitudinal study the use of CPAP was associated with a favorable impact on eGFR decline over the follow-up (median -1.4% [IQR: -7.7–5.2%] vs -5.3% [-16.5–2.7%] vs -7.7% [-15.9 to -1.8%] vs -10.0% [-17.2–2.3%]) for no OSA versus mild OSA versus moderate-to-severe OSA CPAP-compliant versus moderate-to-severe OSA noncompliant with CPAP, respectively (p = 0.01 for the trend) [139]. In a study of Japanese patients with T2D, ODI ≥5 was independently associated with microalbuminuria in women but not in men after adjustment for confounders [140]. A cross-sectional study found that patients with OSA were more likely to have diabetic neuropathy (OR: 2.82; 95% CI: 1.44–5.52) and foot insensitivity (OR: 3.97; 95% CI: 1.80–8.74) compared with those without OSA [106]. Hence, there seems to be an association between OSA and microvascular complications in patients with T2D and early longitudinal studies suggest that OSA plays a role in the progression of DR and DN and that CPAP might have a favorable impact on reducing the progression of these complications. However, further well designed longitudinal studies and RCTs assessing the impact of OSA and its treatment on the progression of microvascular complications in patients with T2D are needed.

• OSA & sleepiness, physical activity & erectile dysfunction in patients with T2D

Several studies showed that OSA was associated erectile dysfunction and that erectile dysfunction severity was associated with the severity of OSA and the nocturnal hypoxaemia [141]. However, causality has not been proved due to the lack of longitudinal studies and convincing data from RCTs [141]. In one small RCT (n = 27), one month of CPAP improved erectile function (assessed by the 5-item international index of erectile function) compared with the control group [142]; but the control group was in 'no treatment' rather than sham CPAP and hence it is difficult to draw firm conclusions as the study-outcome was self-reported and the study was not blinded [141]. RCTs comparing the effect of CPAP to Sildenafil showed that both improved erectile function but Sildenafil was superior to CPAP [141,143–145].

There are no RCTs that assessed the impact of CPAP on erectile dysfunction in patients with T2D but one uncontrolled study showed that CPAP for 3 months had no effect on sexual function in 35 men with T2D but improved excessive daytime sleepiness (measured by ESS) and self-reported physical activity [146].

Future perspective

There is still much to know about the impact of OSA in patients with T2D and this research field is still in relatively early stages. Most of the current literature in patients with T2D consist of cross-sectional studies showing associations rather than causation, with limited data from longitudinal studies and RCTs. In addition, most of the research focussed on the impact of OSA and its treatment on glycemic measures with the impact of OSA on other diabetes-related outcomes gaining momentum only recently. I would expect that over the next few years there will an expansion in the studies and RCTs assessing the impact of OSA and CPAP on metabolic and vascular outcomes in patients with T2D, with particular focus on blood pressure, cardiovascular disease and microvascular complications. In addition there is a need to understand the natural history of OSA in patients with T2D and how the outcomes might differ whether the patients had OSA prior to or after the development of T2D. Future studies will also examine how the impact of OSA might vary in relation to diabetes duration. Studies examining how to screen for OSA in patients with diabetes are also ongoing. Future RCTs will assess the impact of OSA treatment in patients with prediabetes and whether CPAP can reduce T2D incidence. Although beyond the scope of this paper, recent data from patients with T1D suggest that the impact of OSA might be similar to that in patients with T2D and I would expect more studies in patients with T1D to be conducted.

Summary & conclusion

OSA is a risk factor for incident T2D and very common in patients with T2D and most of the patients remain undiagnosed. OSA can be asymptomatic or present with a variety of non-specific symptoms that are common in patients with T2D such snoring, sweating, nocturia, tiredness and erectile dysfunction. Hence a high index of suspicion is required to diagnose OSA in patients with T2D. OSA in patients with T2D is associated with hypertension, cardiovascular disease, microvascular complications and somnolence. OSA is also associated

with the progression of diabetic retinopathy and nephropathy. CPAP treatment was shown to lower BP and might have a favourable impact on cardiovascular disease and the progression of retinopathy and nephropathy in patients with T2D. In addition, CPAP might improve daytime sleepiness and physical activity in patients with T2D. Further well designed longitudinal studies and RCTs are needed to assess the impact of OSA and CPAP on diabetes-related metabolic and vascular outcomes. However, patients with T2D and excessive daytime sleepiness or other OSA-related symptoms should be examined for the presence of OSA and offered treatment accordingly.

Disclaimer

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• **An excellent article about OSA epidemiology.**

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