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Obstructive sleep apnoea

Tahrani, Abd

DOI:

[10.15277/bjd.2016.088](https://doi.org/10.15277/bjd.2016.088)

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Document Version

Peer reviewed version

Citation for published version (Harvard):

Tahrani, AA 2016, 'Obstructive sleep apnoea: A diabetologist's perspective', *The British Journal of Diabetes & Vascular Disease*, vol. 16, no. 3, pp. 107-113. <https://doi.org/10.15277/bjd.2016.088>

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Checked 07/10/2016

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Review article

Obstructive Sleep Apnoea: A Diabetologist's Perspective

Abd A Tahrani MD, MRCP, MMedSci, PhD

Institute of Metabolism and Systems, School of Clinical and Experimental Medicine, University of Birmingham, Birmingham, UK

Department of Diabetes and Endocrinology, Birmingham Heartlands Hospital, Birmingham, UK

Corresponding author:

Dr Abd A Tahrani

Department of Diabetes and Endocrinology,

Birmingham Heartlands Hospital

Birmingham B9 5SS

Abd.tahrani@nhs.net

Word count: 2767

The author declares no conflict of interests

Disclosure: Abd A Tahrani is a clinician scientist supported by the National Institute for Health Research (NIHR) in the UK. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the NIHR or the Department of Health. No funding was received for the publication of this article.

Key words: obstructive sleep apnoea, type 2 diabetes, hypertension, cardiovascular disease, hyperlipidaemia, quality of life.

Abstract

Obstructive sleep apnoea (OSA) is very common in patients with Type 2 diabetes (T2D) which is unsurprising given that obesity is a major risk factor for both conditions. OSA has been associated with impaired quality of life, many cardiovascular disease risk factors and cardiovascular disease in general.

Continuous positive airway pressure (CPAP) treatment has beneficial impacts on CVD risk factors and CVD. However, the true impact of OSA in patients with T2D remains unclear. The International Diabetes Federation (IDF) recommended routine screening for OSA in patients with T2D but two-thirds of diabetes healthcare professionals were unaware of these recommendations. The aim of this review is to attempt to answer the following questions: is OSA diagnosis and treatment important in patients with T2D and why? Therefore what is the relevance of OSA to the practicing Diabetologist?

Abbreviations

AHI: Apnoea hypopnea index

BMI: Body mass index

BP: Blood pressure

CAD: Coronary artery disease

CI: Confidence interval

CPAP: Continuous positive airway pressure

CVD: Cardiovascular disease

DN: Diabetic nephropathy

DR: Diabetic retinopathy

ED: Erectile dysfunction

EDS: Excessive daytime sleepiness

ESS: Epworth sleepiness score

HIF-1: Hypoxia-inducible factor-1

IR: insulin resistance

NAFLD: Non-alcoholic fatty liver disease

NASH: Non-alcoholic steatohepatitis

ODI: Oxygen desaturation index

OGTT: Oral glucose tolerance test

OR: Odds ratio

OSA: obstructive sleep apnoea

QOL: Quality of life

SREBP-1: Sterol regulatory element-binding protein

T2D: Type 2 diabetes

Introduction

OSA affects 17–26% of men and 9–28% of women in population-based epidemiologic studies.¹ It is characterised by upper airway instability during sleep that causes recurrent complete or partial upper airway obstruction resulting in recurrent episodes of either complete (apnoea) or partial (hypopnea) cessation of airflow.² Apnoeas and hypopneas are associated with recurrent oxygen desaturations, cyclical changes in intra-thoracic pressure (as the patient attempts to breath against a blocked airway), BP, heart rate and sympathetic activity and recurrent micro-arousals (due to attempts to open the obstructed airways) that cause sleep fragmentation and disturbs the sleep architecture.² An AHI (Apnoea hypopnea index) represents the average number apnoea and hypopnea episodes/hour during sleep: ≥ 5 events/hour is consistent with the diagnosis of OSA,^{2,3} while AHI cut offs of 15 and 30 indicate moderate and severe OSA.⁴ Other measures of OSA include the ODI (Oxygen Desaturation Index), the average number of oxygen desaturations/hour of sleep (3% or 4% depending on the definition used), the lowest nocturnal oxygen saturations and the time spent with oxygen saturation $<90\%$. Weight loss and CPAP are the mainstay treatments of OSA. Mandibular advancement devices can also be used in patients with mild OSA or those intolerant to CPAP.

Snoring and witnessed apnoeas are common symptoms of OSA, with snoring reported in 95% of patients.² EDS, though associated with OSA, seems to have stronger associations with depression and the metabolic syndrome.^{2,5} Other symptoms such as choking, insomnia, nocturia, sweating, fatigue, morning headache, erectile dysfunction and autonomic symptoms have been reported.^{2,6} Many of these are also common in T2D and contribute to the burden of disease. OSA should be

considered as a cause of such symptoms in patients with T2D after ruling out hypo or hyper glycaemia as CPAP treatment can improve these symptoms.

Obesity is a common risk factor for OSA and T2D,⁷ and the prevalence of OSA is high in people with type 2 diabetes (8.5–85%, with 23.8–70% for moderate-to-severe OSA).⁸⁻¹⁴ This wide range reflects differences in the population examined (primary vs. secondary care, ethnicities, gender, obesity etc.), the methods used to diagnose OSA (patients' records, questionnaires, oximetry, portable multi-channel cardiovascular monitoring devices or “gold standard” polysomnography) and the OSA definitions used (AHI vs. ODI, different cut-offs)^{4;14}. It is not clear, however, whether the prevalence of OSA in patients with T2D is higher than expected for patients with similar adiposity but without T2D. A recent cross-sectional analysis of the European Sleep Apnea Cohort (ESADA; n=6,616) suggested that T2D prevalence, adjusted for obesity and other potential confounders, increased with worsening OSA: odds ratios (OR, 95%CI) were 1.33 (1.04-1.72) for mild OSA, 1.73 (1.33-2.25) for moderate OSA and 1.87 (1.45-2.42) for severe OSA (p<0.001).¹⁵

In 2008, the International Diabetes federation (IDF) recommended routine screening for OSA in patients with T2D,¹⁶ but two-thirds of diabetes healthcare professionals were unaware of these recommendations or that the local diabetes guidelines did not incorporate assessment for OSA in those at risk.¹⁷ Nonetheless, the impact of OSA in patients with T2D, how to screen and the benefits of screening are still unclear.

The impact of OSA on glucose metabolism, and pre-diabetes and the consequences of having OSA in general population studies have been reviewed elsewhere.^{4;18} The aim of this article is to attempt to answer the following questions: is OSA diagnosis and treatment is important in patients with T2D and why? What is the relevance of OSA to the practicing Diabetologist?

OSA is a risk factor for T2D

Many cross-sectional studies in the general population¹⁹⁻²⁸ and patients with T2D^{29;30} showed an association between OSA and IR, but others did not.³¹⁻³³ These conflicting results are partly due to variation in the population examined, sample size (studies that did not show an association were smaller)¹⁴ or because of variation in excessive daytime sleepiness (EDS), which is associated with IR.^{34;35} Obesity did not explain fully the association between OSA and IR; many studies adjusted for obesity measures, OSA was associated with IR in lean men, and OSA can be caused by conditions other than obesity (e.g. acromegaly).³⁶⁻³⁸

One longitudinal study showed that OSA, AHI, ODI and minimal nocturnal oxygen saturations were independent predictors of worsening IR (>75th percentile of change in HOMA-IR) over an 11-year

follow-up after adjustment for age, baseline BMI, hypertension, BMI change over follow-up and CPAP³⁹.

The impact of OSA on β -cell dysfunction in humans is limited. A cross-sectional study showed that OSA was associated with impaired β -cell function in patients with³⁰ or without diabetes.⁴⁰

In addition, OSA is associated with NAFLD and NASH^{27;41}.

OSA predicts the development of incident T2D independently of age, obesity or other confounders^{39;42-46} and 8 hours/night of CPAP improved post-load glycaemia (OGTT) insulin sensitivity, 24 h BP and norepinephrine levels in a randomized, placebo-controlled trial.⁴⁷ However, this study was conducted in the laboratory environment to ensure the high compliance with CPAP and the effects of CPAP on the incidence of T2D in uncontrolled settings remains to be determined.

OSA is associated with worse glycaemic control in patients with T2D

Cross-sectional studies show that OSA is associated with poorer glycaemic control, despite adjustments for age, sex, race, BMI, number of medications, exercise, diabetes duration and total sleep time.^{15;48-50} Lower nocturnal oxygen saturations were associated with higher HbA1c values in one study.⁵¹ but elsewhere there was no association between OSA and HbA1c,⁵² likely because only 22% of participants had full polysomnography and the duration of the sleep study was just 4 hours.⁵³ Prospective studies assessing the impact of OSA on glycaemic measures longitudinally in patients with T2D are lacking.

OSA is associated with hypertension

Extensive epidemiological studies and interventional trials in the general population, but only limited data in patients with T2D, have associated OSA with hypertension and non-dipping BP.^{4;18;54} The Wisconsin Sleep Cohort Study Longitudinal found adjusted ORs for incident hypertension between 1.42 and 2.89 with increasing AHI (vs. AHI=0 at baseline, $p=0002$ for the trend).⁵⁵ Long-term (7 years) mild and moderate OSA (vs. AHI <5) increased the risk of incident nocturnal non-dipping BP about 3-fold and 4-fold, respectively in a subgroup of patients.⁵⁶ A large, cross-sectional study showed that OSA was more prevalent in T2D patients with awake BP $\geq 135/85$ mmHg or asleep BP $\geq 120/70$ mmHg, compared with lower BP⁵⁷, suggesting a link between OSA and hypertension in T2D.

OSA is associated with hyperlipidaemia

A mechanistic link between OSA and hyperlipidaemia is plausible as chronic intermittent hypoxia could lead to the generation of stearyl-coenzyme A desaturase-1, oxidative stress, peroxidation of lipids and sympathetic activation.⁵⁸ However, cross-sectional studies were not consistent mainly due to differences in the population examined, studies designs and the impact of CPAP.^{58;59} A meta-analysis of 64 studies showed that OSA was associated with higher total cholesterol, higher LDL, higher triglycerides and lower HDL, while AHI correlated positively with triglycerides and negatively with HDL levels only.⁵⁹ The association between OSA/AHI and triglycerides is obesity independent.⁶⁰ Longitudinal studies are lacking.

OSA is associated with CVD

General population

OSA has been associated with a larger atherosclerotic plaque volume, with AHI correlating positively with plaque volume.^{61;62} OSA increased the risk of acute myocardial infarction overnight, supporting a role for nocturnal OSA events in the development of CVD.⁶³ Prospective observational studies (3–10 years of follow-up) have shown that OSA predicts the development of incident CVD, with adjusted OR/HR for incident CVD of 1.97–4.9.⁶⁴⁻⁶⁹

Age and gender may modulate the relationship between OSA and incident CVD, as suggested by observational cohort studies in which OSA predicted incident CAD only in men aged <70 years and predicted heart failure in only in men,⁶⁹ or was associated with stroke incidence only in men.⁷⁰ However, a study that included women only showed that untreated OSA predicted a combined outcome of incident stroke and CAD, driven only by increased risk of stroke.⁷¹

In patients with T2D

AHI was associated with history of stroke (adjusted OR 2.57, 95 % CI 1.03–6.42), but not with CAD in a cross-sectional analysis from the Look AHEAD study.⁷² A prospective observational study of 132 consecutive asymptomatic patients with T2D and OSA was associated with incident CAD (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 a median follow-up of 4.9 years.⁷³

OSA is associated with diabetes-related microvascular complications

The link between OSA and microvascular complications is plausible. Intermittent hypoxaemia can result in increased oxidative and nitrosative stress, poly-(ADP-ribose) polymerase (PARP) activation, increased advanced glycation end-products, protein kinase C activation and inflammation in patients

with and without diabetes – all of which can result in endothelial dysfunction and microvascular disease.^{4;11;54}

OSA and diabetic retinopathy (DR)

In Japanese patients undergoing vitreous surgery for advanced DR, lower oxygen saturations were associated with proliferative DR after adjustment for age, HbA1c and hypertension.⁷⁴ Cross-sectional data from the UK suggest that OSA may be independently associated with DR and maculopathy.^{75,76} Longitudinally, patients with OSA were more likely to develop pre-proliferative/proliferative DR than those with T2D.⁷⁶

OSA and diabetic nephropathy

In a cross-sectional study of Japanese patients with T2D, ODI ≥ 5 was independently associated with microalbuminuria in women but not in men after adjustment for confounders.⁷⁷ In another cross-sectional study, OSA was associated with DN in patients with T2D (adjusted OR 2.64, 95%CI 1.13–6.16, $p=0.02$).⁷⁸ Longitudinally, the eGFR decline was greater in patients with vs. without OSA ($p=0.003$). OSA was an independent predictor of study-end eGFR and eGFR decline.

OSA and diabetic neuropathy

A cross-sectional study found that patients with vs. without 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).¹¹

OSA is associated with impaired quality of life (QoL)

Several cross-sectional studies showed that OSA, its severity, and nocturnal hypoxaemia were associated with worse QoL independent of EDS.^{79;80} This association might be modulated by age.⁷⁹

OSA is associated with increased risk of road traffic accidents (RTA)

There is extensive evidence using driving stimulators and insurance databases showing an association between OSA and RTA and that CPAP treatment lowers the risk of RTA in patients with OSA.^{1;81-83} T2D is also associated with increased risk of RTA, but whether having both conditions increases the risk of RTA more than either one alone is unknown.

OSA is associated with erectile dysfunction (ED)

OSA and ED share many risk factors and their severity often goes in parallel.⁸⁴ In one RCT ($n=27$), 1 month of CPAP improved ED, but the findings are difficult to interpret, as the control group in this study was no treatment rather than sham CPAP; also, the study was unblinded and its outcome was

self-reported.⁸⁵ Other uncontrolled/observational studies suggested beneficial effects of CPAP on ED and RCTs showed that sildenafil was superior to CPAP for managing ED.^{84,86-88}

The impact of CPAP on glucose metabolism, CVD and QOL

CPAP improved insulin sensitivity in patients with and without T2D in non-randomised trials,^{89,90} and in meta-analyses,⁹¹⁻⁹³ especially for patients using CPAP >4 hours/night.⁹⁴ Uncontrolled studies in patients with T2D⁹⁵⁻⁹⁹ showed that CPAP improves, postprandial hyperglycemia⁹⁶, glycaemic variability⁹⁷, and/or HbA1c^{96,100}. However, the only available randomized, controlled trial showed no impact of 3 months of CPAP on HbA1c.¹⁰¹ This may have been due to true lack of effect, the sample size, the relatively short duration of treatment and issues with CPAP compliance (3.6 hours/night). Meta-analyses also showed that CPAP did not significantly improve HbA1c in patients with T2D.^{92,102} As the association between OSA and HbA1c seems stronger during REM,¹⁰³ CPAP might have more impact on HbA1c at this sleep stage; CPAP use >4 hours/night may be required to improve HbA1c as REM occurs predominantly towards the end of the night. CPAP therefore cannot be recommended to improve glycaemic control in T2D and well-designed, RCTs are needed.¹⁰⁴

CPAP lowered BP in hypertensive patients with OSA in several RCTs and meta-analyses,¹⁰⁵⁻¹⁰⁷ and resulted in nocturnal dipping in BP in patients with resistant hypertension¹⁰⁷. However, valsartan was superior to CPAP (difference in mean 24 h BP: -7.0 mmHg [95%CI -10.9 to -3.1], p<0.001) in an 8-week randomized, crossover study.¹⁰⁸ CPAP was associated with a mean BP change of -6.81/-3.69 mmHg 9-12 months in a retrospective cohort database study of patients with newly diagnosed OSA and pre-existing hypertension or T2D.¹⁰⁹ CPAP lowered systolic and diastolic BP (149/80 mmHg to 140/73 mmHg [p= 0.005/0.007 in another randomised trial.⁹⁹ As yet, the impact of CPAP on incident hypertension is unclear.¹¹⁰

CPAP reduced total and LDL cholesterol and increased HDL cholesterol but had no effect on triglycerides in a meta-analysis of 29 trials.¹¹¹ Another meta-analysis included only RCTs (n=6) showed that CPAP reduced total cholesterol (particularly in younger, more obese patients, and those who used CPAP for a longer period) without effects on other lipid parameters.¹¹² Three months of CPAP had no effect on the lipids in a RCT in T2D patients, but lipids were well controlled at baseline.⁹⁹ Overall, the impact of CPAP on lipids might be less relevant than that of lipid lowering treatments.

CPAP was associated with lower CVD incidence vs. no CPAP in some observational studies.^{64,65} Randomisation of 723 patients with AHI ≥20 and ESS ≤10 to CPAP vs. no CPAP for 4 years had no impact on the incidence of a composite of hypertension and CVD (OR 0.83, 95 % CI 0.63-1.1; p=0.20).¹¹⁰ However, the combined outcome (but not CVD alone, perhaps due to a lack of events)

was reduced in those who used CPAP ≥ 4 hours/night (OR 0.72, 95 % CI 0.52–0.98; $p=0.04$). The impact of CPAP on CVD in patients with T2D remains unknown. On one hand, the favourable impact of CPAP on CVD risk factors suggest that CPAP might lower CVD; but as the impact of CPAP on CVD risk factors may not be greater than currently available treatments then CPAP might not have an additional benefit. RCTs are again needed to answer this question.

The impact of CPAP on microvascular complications in patient with T2D is limited to a small number of observational studies. In a cohort study from the UK, patients who were more compliant with CPAP had lower progression of DR.⁷⁶ CPAP may support improved functionality rather than actual change in macular oedema.¹¹³ A RCT assessing the impact of CPAP on maculopathy is currently ongoing. CPAP was also associated with less eGFR decline in an observational study from the UK.⁷⁸

Uncontrolled studies suggest that 2–6 months of CPAP might improve vitality, social functioning, mental health, physical health, and levels of independence, with the magnitude of improvement related to the baseline QoL impairment rather than OSA severity.^{80;114} However, another study found that the improvement in QoL on CPAP was similar irrespective of compliance.¹¹⁵ Data in T2D are lacking.

Summary and conclusions

OSA is very common in patients with T2D and is associated with impaired QoL, ED, CV risk factors, CVD and microvascular complications in patients with and without T2D. However, convincing evidence from RCTs in patients with T2D that CPAP treatment has favourable impacts on CVD, microvascular complications or QOL are still lacking. Evidence from general populations suggests that CPAP improves hypertension, hyperlipidaemia, insulin resistance, QOL and CVD. In addition, OSA symptoms are common in patients with T2D and CPAP will improve these symptoms.

Most Diabetologists do not check for OSA in patients with T2D, despite its high prevalence in this population and despite a recommendation to do so by the IDF since 2008. This is further complicated with lack of consensus regarding the best way to screen for OSA in patients with T2D and the lack of data regarding the impact of CPAP and cost-effectiveness; which raises further challenges to diabetologists. However, and regardless of the impact of CPAP on diabetes-related outcomes, it is important to remember that OSA lowers the risk of road traffic accidents. In addition, Diabetologists should also be vigilant to diagnose OSA in patients with T2D in which CPAP might have a favourable impact such as patients who have OSA-related symptoms or patients with resistant hypertension or significant insulin resistance. Ongoing RCTs will clarify the impact of CPAP on diabetes-related outcomes, particularly glycaemic control and micro and macro vascular disease.

In addition, several studies are examining the role of several biomarkers to aid screening for OSA in patients with T2D.

Key points:

- OSA is common in both the general population and in those with type 2 diabetes, with an association with obesity.
- The IDF recommends screening patients with type 2 diabetes for OSA but practice varies and there is no consensus approach.
- CPAP treatment has an impact on BP, cholesterol, insulin resistance, quality of life and possibly cardiovascular disease but the evidence in patients with T2D is limited.

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