



# Obstructive sleep apnoea and type 2 diabetes: whose disease is it anyway?

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## Introduction

By 2025 it is estimated that over four million people in the UK will have diabetes. Approximately 10% of the UK's National Health Service (NHS) annual budget was spent on people with diabetes in 2009/2010.<sup>1</sup> The rise in diabetes is largely driven by the rise in obesity. Almost two in every three people in the UK are overweight or obese. Parallel with the rise in obesity and diabetes, there has been a rise in patients with obstructive sleep apnoea (OSA). The Wisconsin Sleep Cohort Study,<sup>2</sup> a pioneering study of OSA, reported that OSA affected 2–4% of the general population in 1993. More recent reports, taking into account the increased prevalence of obesity, estimate that up to 17% of adults have OSA. Importantly, OSA is common in patients with type 2 diabetes mellitus (T2DM). This prevalence varies depending on the population and setting of the study but ranges from 20% to as much as 80%.

While obesity is an important contributor to OSA, less than 50% of OSA is attributable to obesity. Other factors which are also important in OSA include age (older individuals), gender (men greater than women), ethnicity (African Americans and Hispanics), and craniofacial abnormalities. OSA has been associated with polycystic ovarian syndrome, hypothyroidism, and less common endocrine conditions such as acromegaly. Smoking and alcohol consumption can exacerbate OSA. Several gene polymorphisms have been associated with OSA in line

## ABSTRACT

The association between type 2 diabetes mellitus (T2DM) and obstructive sleep apnoea (OSA) is increasingly recognised. Both conditions are rising in prevalence due to the increased prevalence in obesity, which plays a key role in both disorders. Emerging evidence suggests that T2DM and OSA may also be related independently of obesity. This raises the possibility that identifying and treating OSA in patients with diabetes could have an important impact on diabetes control and cardiovascular health. This article is a summary of the implications of OSA for patients with T2DM. Copyright © 2011 John Wiley & Sons.

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## KEY WORDS

type 2 diabetes (T2D); obesity; obstructive sleep apnoea (OSA)

with a complex genetic condition. Obesity is a common risk factor for both diabetes and OSA. However, emerging evidence suggests a relationship between OSA and diabetes independent of obesity.

OSA belongs to a spectrum of breathing disorders during sleep (sleep-disordered breathing) that range from simple snoring to complete cessation of breathing. OSA is characterised by frequent abnormal pauses in breathing during sleep. These pauses are obstructive in nature and occur despite respiratory effort by the patient. OSA is associated with repetitive blood oxygen desaturation because of lack of airflow into the lungs. Obstructive events during sleep are associated with arousals that are often unnoticed by the patient. These arousals result in fragmented sleep that causes excessive daytime sleepiness (EDS). This increases the risk of road and workplace accidents. The symptoms of OSA include snoring, witnessed breath-holds, gasping and choking, fatigue, reduced alertness,

nocturia, morning headaches, reflux oesophagitis, poor memory, low mood and gendernal dysfunction. Some of these symptoms are also seen in poorly controlled diabetes, resulting in the possibility of OSA being forgotten in patients with diabetes. Severe OSA can be potentially life threatening if left untreated, resulting in heart failure and arrhythmias. There is increasing evidence linking OSA to vascular, metabolic, haematological and genetic markers associated with increased risk for cardiovascular disease.

Identifying patients with OSA in the diabetes clinic tends not to occur because of lack of awareness of the relationship between the two conditions. OSA questionnaires are not very useful either, because they have not been designed for the diabetes population. Also, diabetes patients may not specifically report sleepiness. Potential indicators of OSA in diabetes patients include frequent headaches, acid reflux disease, impotence, poor glycaemic control, and uncontrolled hypertension.

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OSA may also be more common in patients with microvascular complications, particularly maculopathy. Since all of these are non-specific, or common in the diabetes patient population, screening is necessary to identify patients at risk.

The measure of OSA is the apnoea-hypopnoea index (AHI). This is calculated by the number of apnoeas (complete cessation of breathing) added to the number of hypopnoeas (reduced airflow) per hour of sleep. OSA is associated with an AHI of >5/hour of sleep. Classically, OSA is diagnosed by an overnight sleep study (polysomnography). New devices, however, can help diagnose OSA without the need for a full sleep study. These devices range from simple oximetry to devices that combine oximetry with measures of airflow and/or chest and abdominal movements. While these simpler devices are useful for straightforward cases, more complex cases still require polysomnography. In the sleep clinic, patients referred for sleep studies are likely to be at high risk for diabetes and should be screened for diabetes and other cardiovascular risk factors. Although HbA<sub>1c</sub> may be a useful screening tool, its utility has not been studied in this population group with high body mass index (BMI) and OSA.

Currently, the main treatment for OSA is continuous positive airway pressure (CPAP) therapy,<sup>3</sup> combined with weight loss, reduced alcohol and sedative intake, and also lifestyle change to address adiposity. A 10% weight gain can result in up to 30% increase in AHI. A similar modest weight loss can improve or resolve OSA. Lifestyle change with weight loss is very important in improving or resolving OSA, but difficulty in maintaining lifestyle change means that many patients with OSA need specific treatment with CPAP. Less common approaches include mandibular advancement splints and surgery. CPAP provides a pneumatic splint to maintain upper airway patency, preventing collapse. A Cochrane review<sup>4</sup> investigated the symptomatic benefits of CPAP in OSA and listed them as: improved sleepiness; clearer thinking and concentration;

improved snoring and pauses in sleep; better daytime function; improved psychological wellbeing and better quality of life. CPAP treatment is cost-effective and has been approved by the National Institute for Health and Clinical Excellence for symptomatic moderate or severe OSA (AHI ≥15/hour).

#### OSA, diabetes and the metabolic syndrome

Recently, the overlap between T2DM and OSA has been more widely recognised. Animal and human models of intermittent hypoxia have been shown to demonstrate insulin resistance. This is seen physiologically with altitude and pathologically in chronic conditions such as chronic obstructive pulmonary disease. The Wisconsin Sleep Cohort Study<sup>5</sup> has shown that diabetes is more prevalent in patients with sleep-disordered breathing (SDB, which includes OSA) and this relationship is independent of other risk factors. However, it was not clear whether SDB is causal in the development of diabetes.

A study looking at the association of OSA with the metabolic syndrome found that OSA was independently associated with increased systolic and diastolic blood pressure, higher fasting insulin and triglyceride levels, decreased HDL cholesterol, increased cholesterol:HDL ratio, and a trend towards higher HOMA (homeostatic model assessment; a measure of insulin resistance) values. The study investigators also found that metabolic syndrome was 9.1 times (95% confidence interval 2.6, 31.2;  $p < 0.0001$ ) more likely to be present in patients with OSA.<sup>6</sup>

Lam *et al.*<sup>7</sup> established that subjects, in a community-based cohort, with OSA, defined as an AHI of ≥5 (37% of the study sample) had a five-fold risk of having the metabolic syndrome. They also found an increasing association with the metabolic syndrome as the severity of OSA increased.

Gruber and colleagues found that patients with OSA were about six times more likely to have metabolic syndrome than patients without OSA, adjusted for BMI, smoking

and age, but OSA was not independently associated with the insulin resistance state.<sup>8</sup>

A major problem with epidemiological studies of the relationship between OSA, diabetes and metabolic syndrome is taking into account the impact of visceral adiposity which is poorly measured by BMI.

#### Effects of CPAP treatment on type 2 diabetes

There has been much ongoing discussion on the potential favourable effects of CPAP treatment on diabetes and the metabolic syndrome. There is conflicting evidence on the effects of CPAP treatment on insulin sensitivity. A small, uncontrolled study with 40 patients found that insulin resistance improved with CPAP.<sup>9</sup> However, this study was confined to lean patients with a BMI <30 kg/m<sup>2</sup>. Babu *et al.*<sup>10</sup> used a continuous glucose monitoring system and showed a decrease in postprandial blood glucose after 30–90 days of CPAP treatment. They also noted a decrease in HbA<sub>1c</sub> in those with a baseline level >7% (53 mmol/mol) and that the decrease in HbA<sub>1c</sub> correlated with days on CPAP if compliance was more than 4 hours. In a randomised controlled trial (RCT) of CPAP treatment on insulin sensitivity in Chinese male patients with OSA, Lam *et al.*<sup>7</sup> noted a decrease in HbA<sub>1c</sub> of diabetic patients with OSA on CPAP. Insulin sensitivity was improved in patients on CPAP that was maintained at 12 weeks, but only for those with a BMI ≥25 kg/m<sup>2</sup>.

On the other hand, a double-blind RCT of therapeutic and placebo CPAP, for three months in men with T2DM and OSA, found no significant improvement in HbA<sub>1c</sub> or insulin resistance measured by euglycaemic clamp and HOMA. However, patients in this study receiving therapeutic CPAP experienced significant improvements in their subjective and objective sleepiness and sleep apnoea quality of life scores, indicating that CPAP was effectively treating their OSA. This study was, however, carried out in patients with relatively good blood glucose control which may have masked any effects of CPAP. Another trial of CPAP versus sham-CPAP on





metabolic syndrome found that CPAP was associated with a non-significant 7.3% (-20, 7.5%; 95% CI) improvement in impaired glucose tolerance.<sup>11</sup>

Therefore, there is considerable disagreement among studies on the effects of CPAP treatment on glycaemic control because of different patient population groups, sample size and control groups. Most studies have been uncontrolled or have had inadequate control of confounding factors. Differing techniques have been used to assess glucose metabolism. Also, not all studies report on CPAP adherence. There is, therefore, a need for longer-term, well designed, large-scale RCTs. CPAP adherence will be an important issue in these studies.

### Effect of CPAP therapy on cardiovascular disease

One of the well established risks of diabetes is cardiovascular disease (CVD). There is a need to understand and address novel factors such as OSA that may be contributing to CVD in diabetes patients. Peker *et al.* have demonstrated that efficient treatment of OSA with CPAP reduces the excess risk of CVD.<sup>12</sup> They also found an increased incidence of CVD in incompletely treated OSA, which advocates that active treatment should be readily considered in sleep-disordered breathing.

OSA has a causative relationship with hypertension. This has been demonstrated by Somers *et al.*<sup>13</sup> who found that, during an apnoea, the obstructed inspiratory efforts led to falls in pleural pressure that are reflected in the blood pressure tracing. At the end of an apnoea, the arousal provoked a rise in blood pressure. The Sleep Heart Health Study<sup>14</sup> also found a modest but clear independent association between OSA and hypertension in which the prevalence of hypertension increased with increasing AHI. Several clinical trials<sup>15–21</sup> have addressed the effects of CPAP on daytime blood pressure in patients with OSA. However, these studies have suffered from a serious flaw in design as the great majority of patients studied were normotensive

while awake so have shown trivial effects of CPAP on blood pressure. One study found that one-year CPAP treatment slightly reduced blood pressure in hypertensive patients with severe OSA but without daytime hypersomnolence.<sup>22</sup> Although CPAP reduces hypertension in moderate to severe OSA patients and key factors in treatment success are effective therapy and adherence to CPAP, the long-term benefits of CPAP on morbidity and mortality are unknown and require longer-term studies.

Hypertension is a major risk factor for the development of stroke, congestive heart failure (CHF) and coronary artery disease (CAD). The probability of CAD is increased in patients with sleep apnoea. The mechanisms involved in disease development, progression, and symptoms of CAD include: changes in intrathoracic pressure; recurrent hypoxia and reoxygenation and fluctuating autonomic activity. Fluctuation in heart rate and angina may be triggered by blood pressure change, and increased oxygen demand and reduced oxygen supply. In patients with CAD, event-free survival is increased in treated compared with untreated groups with OSA.<sup>23</sup>

Sleep-related periodic breathing with recurrent episodes of apnoea and hypopnoea is also known to occur in patients with heart failure.<sup>24–27</sup> The consequences of sleep apnoea and hypopnoea, such as arterial oxyhaemoglobin desaturation and excessive arousals, which result in sympathetic activation, could further contribute to the morbidity and mortality of heart failure patients.<sup>28,29</sup> In a study looking at sleep apnoea and heart failure in men, Javaheri and colleagues<sup>25</sup> found that central sleep apnoea occurred in 40% and obstructive sleep apnoea in 11% of their patients, and that both central and obstructive forms of sleep apnoea resulted in sleep disruption and arterial oxyhaemoglobin desaturation. They also found that atrial fibrillation, ventricular arrhythmias, and low left ventricular ejection fraction were associated with sleep apnoea in heart failure. In the Sleep

### Key points

- Obstructive sleep apnoea (OSA) and diabetes are closely related conditions
- Obesity is a common factor for both conditions but there is evidence for a potential independent association between OSA and diabetes
- Identifying and treating OSA in patients with diabetes could have an important impact on diabetes control and cardiovascular health

Heart Health Study,<sup>14</sup> the presence of OSA was associated with a 2.38 relative odds for CHF independent of other known risk factors. Some small case series and uncontrolled trials have suggested that treatment of OSA with CPAP in patients with idiopathic cardiomyopathy led to significant improvements in heart function.<sup>30–32</sup> An RCT of OSA in patients with CHF demonstrated significant three-month improvements in cardiac function and attenuation of sympathetic nerve activity associated with reduced hypoxaemia with nasal CPAP treatment. Kaneko *et al.*<sup>33</sup> also found that left ventricular ejection fraction (LVEF used as evidence of systolic dysfunction) improved by 9% with CPAP in a one-month controlled trial involving 24 patients with OSA and CHF.

OSA has been suggested as a modifiable and independent risk factor for stroke as defined by international guidelines.<sup>34,35</sup> The Sleep Heart Health Study<sup>14</sup> was the first large-scale, population-based study to examine the potential relationship between sleep apnoea and stroke in 6424 subjects. The presence of OSA was associated with modest, but clear, increased prevalence of stroke. Sleep apnoea is reported to occur in 43–91% of patients who have suffered from a stroke compared with controls who have not had a stroke.<sup>36–40</sup> Yaggi *et al.* have also demonstrated that OSA risk factor for stroke is independent of gender, BMI, diabetes and hypertension.<sup>41</sup> Five-year survival post stroke has also been shown to be improved among those patients who are compliant with CPAP.<sup>42</sup>



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**Diabetes-OSA clinical pathways**

As discussed, there are strong links between OSA, diabetes, obesity and CVD. The International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention has called for action to be taken among the diabetes community to address the areas of awareness, clinical practice and research with regard to OSA and diabetes. With regard to awareness, the IDF recommends that all health professionals involved with diabetes or OSA should be educated about the links between the two conditions. Health policy makers and the general public also need to be made more aware of OSA and the significant financial and disability burden that it places on both individuals and societies. Health professionals working with both T2DM and OSA patients should adopt clinical practices to ensure that a patient presenting with one condition is considered for the other. Also, health professionals should aim to develop locally appropriate clinical pathways for both T2DM and sleep services. Collaboration between services provided by health care professionals is vital in order to develop integrated pathways to ensure that patients get the appropriate care.

**Conclusion**

OSA and diabetes are closely related conditions with links between the two disorders now more widely acknowledged. Obesity is a common factor for both conditions but there is evidence for a potential independent association between OSA and diabetes. Both the sleep disruption and intermittent hypoxia that occur with OSA can influence glucose metabolism. Emerging evidence also suggests that OSA and intermittent hypoxia could play a role in diabetic retinopathy, particularly maculopathy.

There is a major need to address the rise in both diabetes and OSA. The International Diabetes Federation has recommended that we need more intervention studies and also resource development to tackle this rise. They advocate more research in the following areas: epidemiological studies of prevalence of OSA patients with type 2 diabetes and metabolic syndrome in (1) children with obesity, especially those with type 2 diabetes, (2) different ethnic groups, and (3) gestational diabetes and pre-eclampsia. More studies are needed on the effects of OSA on (1) insulin secretion, insulin resistance, mitochondrial

function and inflammatory markers, and (2) complications of type 2 diabetes. The way forward is through collaboration between health care and service providers and researchers across all levels of care.

**Declaration of interests**

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References are available at [www.practicaldiabetesinternational.com](http://www.practicaldiabetesinternational.com).

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**Association of British Clinical Diabetologists Spring Meeting**, Hilton Birmingham Metropole, Birmingham, UK. **Contact:** Elise Harvey; tel: +44 (0)1666 840589, **email:** [eliseharvey@redhotirons.com](mailto:eliseharvey@redhotirons.com), **website:** [www.diabetologists-abcd.org.uk](http://www.diabetologists-abcd.org.uk)

**21 May 2011**

**Diabetic foot and lower limb care for the 21st century: what every patient has the right to expect**, King's College Hospital, London, UK. **Contact:** Christian Pankhurst; **email:** [diabeticfootcomplications@yahoo.com](mailto:diabeticfootcomplications@yahoo.com)

**24–26 May 2011**

**The Royal College of Ophthalmologists Annual Congress**, Birmingham, UK. **Contact tel:** +44 (0)207 935 0702, **website:** [www.rcophth.ac.uk](http://www.rcophth.ac.uk)

**25–28 May 2011**

**18th European Congress on Obesity**, Istanbul, Turkey. **Contact:** EASO Secretariat; **tel:** +44 (0)20 7691 1900, **email:** [mpresutto@iaso.org](mailto:mpresutto@iaso.org), **website:** [www.easoobesity.org/index.htm](http://www.easoobesity.org/index.htm)

**6–9 June 2011**

**British Renal Society Conference 2011**, ICC, Birmingham, UK. **Contact email:** [brs@britishrenal.org](mailto:brs@britishrenal.org), **website:** [www.britishrenal.org](http://www.britishrenal.org)

**10 June 2011**

**Diabetic Foot Master Class**, King's College Hospital, London, UK. **Contact:** Christian Pankhurst; **email:** [diabeticfootmasterclass2011@yahoo.com](mailto:diabeticfootmasterclass2011@yahoo.com)

**24–28 June 2011**

**American Diabetes Association 71st Scientific Sessions**, San Diego Convention Center, San Diego, USA. **Contact email:** [adareg@cmrus.com](mailto:adareg@cmrus.com), **website:** [www.diabetes.org](http://www.diabetes.org)

**6–8 July 2011**

**Heart UK Annual Conference 2011**, The University of Warwick, UK. **Contact:** Wheldon Events; **tel:** +44 (0)1543 503 322, **email:** [wheldonevents@btconnect.com](mailto:wheldonevents@btconnect.com), **website:** [www.heartuk.org.uk](http://www.heartuk.org.uk)

**9–10 September 2011**

**16th FEND Annual Conference**, Lisbon, Portugal. **Contact:** Kristin de Backer; **tel:** +32 3449 4374, **email:** [registration2011@fend.org](mailto:registration2011@fend.org), **website:** [www.fend.org](http://www.fend.org)

**12–16 September 2011**

**47th Annual Meeting of the European Association for the Study of Diabetes (EASD)**, Lisbon, Portugal. **Contact:** EASD Secretariat; **tel:** +49 211 758 469 0, **email:** [secretariat@easd.org](mailto:secretariat@easd.org), **website:** [www.easd.org](http://www.easd.org)

**19–22 October 2011**

**International Society for Pediatric and Adolescent Diabetes (ISPAD) Conference 2011**, Miami, USA. **Contact:** ISPAD 2011 Conference Secretariat; **email:** [ispad2011@kit-group.org](mailto:ispad2011@kit-group.org), **website:** [www.ispad.org](http://www.ispad.org)

**9–11 November 2011**

**39th Meeting of the British Society for Paediatric Endocrinology and Diabetes**, Mary Ward House, London, UK. **Contact:** Dr Justin Warner, BSPED Secretariat, Euro House, 22 Apex Court, Woodlands, Bradley Stoke, Bristol BS32 4JT, UK; **website:** [www.bsped.org.uk](http://www.bsped.org.uk)

**10–12 November 2011**

**2nd International Diabetes and Obesity Forum (IDOF 2011)**, Istanbul Convention and Exhibition Centre, Turkey. **Contact:** C and C International; **email:** [idof2011-info@candc-group.com](mailto:idof2011-info@candc-group.com), **website:** [www.idof2011.com](http://www.idof2011.com)

**4–8 December 2011**

**International Diabetes Federation World Diabetes Congress**, Dubai International Convention and Exhibition Centre, Dubai, United Arab Emirates. **Contact:** International Diabetes Federation Congress Secretariat; **tel:** +32 2 543 16 31, **email:** [wcd@idf.org](mailto:wcd@idf.org), **website:** [www.worlddiabetescongress.org](http://www.worlddiabetescongress.org)





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