

## Obstructive Sleep Apnea and Type 2 Diabetes

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### Abstract

With the growing prevalence of obesity, the burden of type 2 diabetes is increasing. Obstructive sleep apnea (OSA) is a very common medical condition that is associated with increased risk for cardiovascular disease and mortality. Obesity is a common risk factor for OSA and type 2 diabetes and hence it is not surprising that OSA and type 2 diabetes are interlinked. OSA has been shown to be an independent risk factor for the development of incident pre-diabetes/type 2 diabetes. OSA is also associated with worse glycemic control and vascular disease in patients with type 2 diabetes. However, evidence for the benefits of OSA treatment in patients with type 2 diabetes is still lacking. The aim of this article is to provide an overview of OSA, the relationships between OSA and dysglycemia and the impact of OSA in patients with type 2 diabetes, highlighting recent advances in the field.

### Keywords

Diabetes, sleep apnea, obesity, pre-diabetes, impaired glucose tolerance, hypertension, cardiovascular disease, retinopathy, nephropathy, neuropathy, glycosylated hemoglobin

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Diabetes is a global epidemic with an estimated worldwide prevalence of 8.3 % (382 million) in 2013 that is forecast to rise to 10.1 % (592 million) in 2035.<sup>1</sup> Type 2 diabetes accounts for >90 % of all cases, and costs an estimated 10–12 % of the world's health expenditure in 2010 to 2013.<sup>1–3</sup> In addition to the high prevalence of diabetes, 316 million people have impaired glucose tolerance (IGT) that is projected to increase to 471 million by 2035.<sup>1</sup>

Type 2 diabetes is a complex metabolic disorder in which the interaction between multiple genetic and environmental factors results in a heterogeneous and progressive condition with variable degrees of insulin resistance (IR) and pancreatic  $\beta$ -cell dysfunction.<sup>4</sup> Overweight and obesity are major contributors to the IR.<sup>4–6</sup> When  $\beta$ -cells are unable to secrete sufficient insulin to overcome IR, type 2 diabetes ensues.<sup>4,6</sup>

Obstructive sleep apnea (OSA) is a common disorder characterized by upper airway instability during sleep, resulting in markedly reduced (hypopnea) or absent (apnea) airflow.<sup>7</sup> These apnea/hypopnea episodes are usually accompanied by recurrent oxygen desaturations and cyclical changes in blood pressure (BP) and heart rate and disturbances in sleep architecture such as loss of slow-wave sleep (SWS) and rapid eye movement (REM) sleep.<sup>7</sup>

Although obesity is the main driver for IR and  $\beta$ -cell dysfunction, several aspects of sleep-related disorders have recently emerged as potentially

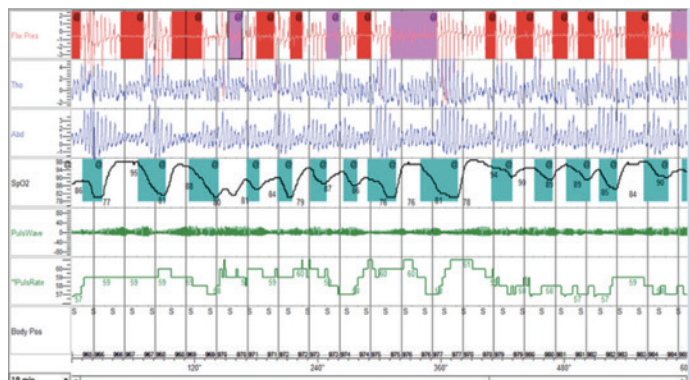
important contributors to IR and to the development of IGT/type 2 diabetes.<sup>8</sup> Short sleep duration and disturbances in the circadian rhythm are associated with IR and increase the risk for type 2 diabetes.<sup>9–12</sup> Hence there is a lot of interest among endocrinologists and sleep specialists to further our understanding of the role of sleep in patients with dysglycemia.

The aim of this paper is to give an overview of OSA and review the evidence for the relationship between OSA and type 2 diabetes with particular focus on more recent studies.

### Obstructive Sleep Apnea Definitions

The American Academy of Sleep Medicine (AASM) guideline has defined an apnea as cessation or  $\geq 90$  % reduction in airflow for a period of  $\geq 10$  seconds; hypopnea has different definitions detailed in the AASM but a commonly used definition is  $\geq 30$  % reduction in airflow for  $\geq 10$  seconds associated with  $\geq 4$  % drop in oxygen saturations.<sup>13</sup> Apneas are classified into obstructive or central, based on the presence or absence of respiratory/abdominal efforts. Examples of apneas and hypopneas can be found in *Figure 1*. The apnea-hypopnea index (AHI) is the average number apnea and hypopnea episodes per hour during sleep and is a marker of OSA severity.<sup>7</sup> An AHI  $\geq 5$  events/hour is consistent with the diagnosis of OSA;<sup>14</sup> however, in the context of research, different studies in the literature used different AHI

**Figure 1: An Example of Apnea (Red), Hypopneas (Pink) and Desaturations (Green) in a Patient with Obstructive Sleep Apnea and Type 2 Diabetes**



Note the the presence of thoracic and abdominal movements indicating the presence of obstructive rather than central sleep apnea.

cut-offs to define OSA including 5, 10, 15, and 30 events/hour. OSA can be classified as mild, moderate, and severe based on AHI 5 to <15, 15 to <30 and  $\geq 30$  events/hours. The respiratory disturbance index (RDI) is another OSA measure that includes the AHI in addition to respiratory effort-related arousal, which is defined as a sequence of breaths characterized by increasing respiratory effort leading to an arousal from sleep, but that does not meet criteria for an apnea or hypopnea.<sup>7</sup> Another measure of OSA is the oxygen desaturation index (ODI), which is the average number of oxygen desaturations per hour during sleep.

## Obstructive Sleep Apnea Epidemiology and Risk Factors

The prevalence of OSA varies considerably between studies, mainly due to differences in the population studied, study designs, and the method and criteria used to diagnose OSA. In addition, as obesity and age are major risk factors for OSA, it is likely that OSA prevalence is increasing with the increasing prevalence of obesity and an aging population. It is estimated that 17–26 % of men and 9–28 % of women have OSA and that 9–14 % of men and 2–7 % of women have moderate to severe OSA.<sup>15</sup> This OSA prevalence is reported from studies that used a two-stage sampling design that allows some degree of estimate of the ‘self-selection’ bias, which is usually a significant problem in OSA studies.

Ethnicity and gender have significant impacts on OSA prevalence. Some studies showed a higher adjusted OSA prevalence in Afro-Caribbeans (increased twofold) compared with White Europeans,<sup>15</sup> while others did not confirm this.<sup>16</sup> The Chinese population has a high OSA prevalence (8.8 % in men and 3.7 % in women) despite being less obese than White Europeans,<sup>17,18</sup> which highlights the importance of factors other than obesity (such as upper airway anatomy) in the development of OSA.<sup>19</sup> In South Asians, OSA prevalence varies between 3.7 % in a semi-urban population to 19.5 % in middle-age urban men.<sup>20–22</sup> Men have two to three times increased risk for OSA compared with women:<sup>15</sup> differences in sex hormones, upper airway size and ventilatory control have been implicated in the gender differences.<sup>23,24</sup> OSA prevalence in elderly men is three to six times that in younger men,<sup>15,23,25</sup> however, this age effect

plateaus around the age of 65 years.<sup>16</sup> Changes in pharyngeal anatomy and upper airway collapsibility are likely responsible for the age impact on OSA prevalence.<sup>23</sup>

Excess body weight is by far the most important risk factor for OSA, although not all OSA patients are obese. In the Wisconsin sleep study, each increase in body mass index (BMI) by one standard deviation, resulted in a fourfold increase in OSA prevalence.<sup>26</sup> Weight gain is a strong predictor of developing OSA or worsening of pre-existing OSA<sup>27,28</sup> and weight loss (via lifestyle modifications or surgical intervention) improve/cure OSA.<sup>29,30</sup> Several mechanisms might be responsible for the association between obesity and OSA. Obesity can alter normal upper airway mechanics during sleep by increased parapharyngeal fat deposition resulting in a smaller upper airway, altering the neural compensatory mechanisms that maintain airway patency, reducing the functional residual capacity with a resultant decrease in the stabilizing caudal traction on the upper airway and affecting the chemosensitivity to O<sub>2</sub> and CO<sub>2</sub>, which reduces ventilator drive.<sup>31</sup> Other OSA risk factors include current smoking, excess alcohol intake, and genetic factors.<sup>15,23</sup>

## Obstructive Sleep Apnea Pathophysiology

OSA is a very complex disorder, and pathogenesis involves multiple mechanisms (see *Figure 2*). Upper airway size and collapsibility plays an important role; smaller airways are more likely to collapse.<sup>32</sup> The presence of upper airway deficits in patients with OSA is supported by data showing that upper airway muscles (genioglossus) activity is increased in patients with OSA,<sup>33</sup> suggesting that these muscles are compensating for an underlying upper airway deficit<sup>32</sup> and that continuous positive airway pressure (CPAP) treatment improves muscle hyperactivity.<sup>34</sup> Sleep onset is associated with greater reductions in upper airway muscle tone in OSA patients, which explains the occurrence of apnea/hypopnea episodes at sleep onset and during REM sleep.<sup>32</sup> Other factors contributing to OSA pathogenesis include changes in lung volume, abnormalities in ventilatory control and stability, changes in chemosensitivity to CO<sub>2</sub>, and higher arousal thresholds.<sup>32</sup>

## Obstructive Sleep Apnea Clinical Features and Diagnosis

A thorough history and examination are still essential parts of the assessment of patients with OSA despite the fact that several reports have shown the limited value of symptoms in predicting OSA.<sup>35</sup> Snoring is the most common symptom of OSA and only 6 % of OSA patients (or their partners) have not reported snoring.<sup>7</sup> Snoring, however, has a poor predictive value as many snorers do not have OSA.<sup>7</sup> Nonetheless, lack of snoring almost rules out OSA.<sup>7</sup> Witnessed apneas are another important symptom that is usually reported by the partner. However, witnessed apneas do not correlate with disease severity and around 6 % of the ‘normal’ population appear to have experienced apneas without OSA.<sup>7</sup> Other nocturnal symptoms such as choking (which is possibly a ‘proper’ rather than a ‘micro’ arousal to terminate apnea), insomnia, nocturia, and diaphoresis have been reported.<sup>7</sup> Daytime symptoms include EDS, fatigue, morning headache, and autonomic symptoms.<sup>7</sup>

The gold standard to diagnose OSA is polysomnography that typically includes the recording of 12 channels such as electroencephalogram (EEG), electrooculogram (EOG), electromyogram (EMG), oronasal airflow,

chest wall effort, abdominal effort, body position, snore microphone, electrocardiogram (ECG) and oxyhemoglobin saturation.<sup>7</sup> Portable home-based respiratory devices are another alternative.<sup>7</sup> Pulse oximetry is another good way to diagnose sleep apnea but it cannot differentiate between obstructive and central apneas and it has a wide range of sensitivity (31–98 %) and specificity (41–100 %). The AASM recommends use of a type III device as a minimum.<sup>7</sup>

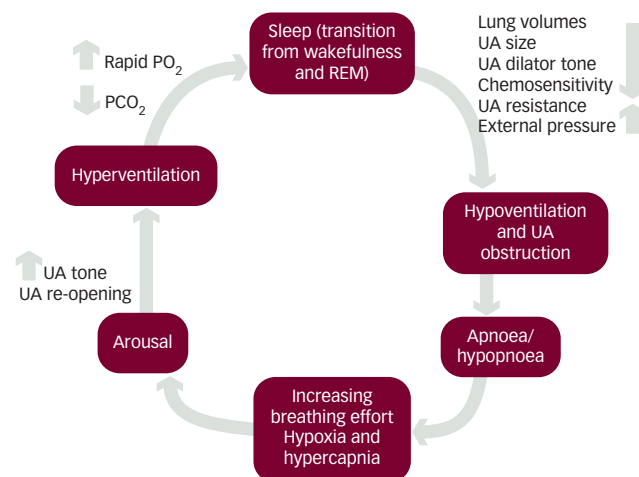
### Obstructive Sleep Apnea as a Risk Factor for Type 2 Diabetes

Several prospective studies have shown an increased risk for type 2 diabetes in patients with OSA and that OSA is an independent risk factor for incident type 2 diabetes after adjustment for age, obesity, and other possible confounders.<sup>36–42</sup> Most of these studies used polysomnography to diagnose OSA, but these included a relatively small number of participants as polysomnography is time-consuming and requires significant resources. The diagnosis of type 2 diabetes in these studies was mostly based on ‘physician diagnosis’ or fasting plasma glucose. However, more recent studies that used oral glucose tolerance tests to assess glycemic status found similar results to other studies (see *Table 1*). A meta-analysis of published studies that used objective measures to diagnose OSA found that moderate to severe (but not mild) OSA was associated with increased risk for developing type 2 diabetes (moderate to severe OSA: relative risk [RR] 1.63, 95 % confidence interval [CI] 1.09–2.45; mild OSA RR 1.22, 95 % CI 0.91–1.63).<sup>43</sup>

The impact of OSA on incident type 2 diabetes is likely to be related to its impact on IR and  $\beta$ -cell dysfunction. While some cross-sectional studies showed an association between OSA and IR,<sup>44–64</sup> others did not.<sup>65–71</sup> Several factors might be responsible for these conflicting results. Studies that did not show such an association typically included fewer participants and were possibly underpowered. Variation in excessive daytime sleepiness (EDS), which has been shown to be associated with IR,<sup>72,73</sup> between study populations might also contribute to the variation in results. Further evidence for the relationship between OSA and IR comes from a study which assessed the impact of OSA on IR (homeostatic model assessment [HOMA]-IR) longitudinally over 11-year follow-up. This showed that OSA, AHI, ODI, and minimal oxygen saturations were independently associated with IR after adjustment for age, baseline BMI, hypertension, BMI change over follow-up, and CPAP treatment.<sup>42</sup> CPAP treatment was shown to lower IR in some studies<sup>74,75</sup> but not in others.<sup>48,65,76–78</sup> However, several meta-analyses showed that CPAP treatment lowers IR,<sup>79,80</sup> particularly in those compliant with treatment and using CPAP >4 hours per night.<sup>81</sup>

Obesity remains a major possible confounder for the relationship between OSA and IR. Recent studies tried to address this matter by reassessing this association in lean individuals.<sup>82,83</sup> Healthy lean men (BMI 22.6 kg/m<sup>2</sup>) with OSA had 27 % lower insulin sensitivity and 37 % higher insulin secretion than age, BMI, family history, and exercise level-matched control after ingestion of a glucose load despite comparable glucose levels between groups.<sup>82</sup> This suggests that OSA in lean men is associated with IR and a compensatory rise in insulin secretion to maintain normoglycemia. Another study showed that OSA was associated with dysglycemia/pre-diabetes in lean but not obese Koreans.<sup>84</sup> Furthermore, in conditions in which IR is not driven by obesity, such as acromegaly, OSA has been associated with IR and dysglycemia.<sup>85</sup> Hence it is likely

### Figure 2: Summary of the Pathogenesis of Obstructive Sleep Apnea



REM = rapid eye movement; UA = upper airway.

that OSA is associated with IR independent of obesity and that this is amenable to treatment with CPAP.

Contrary to the relationship between OSA and IR, the impact of OSA on  $\beta$ -cells is rather limited. *In vitro* and animal studies showed that intermittent hypoxia increases  $\beta$ -cell death, and results in  $\beta$ -cell dysfunction,<sup>86,87</sup> but the intermittent hypoxia used in these studies was greater than that which occurs in humans with OSA. Two studies in humans showed that OSA was associated with  $\beta$ -cell dysfunction in patients with<sup>88</sup> and without type 2 diabetes.<sup>44</sup> Much more data are needed in terms of the longitudinal impact of OSA on  $\beta$ -cells and the impact of CPAP.

### Type 2 Diabetes as a Risk Factor for Obstructive Sleep Apnea

Unlike the well-examined impact of OSA on the risk for developing type 2 diabetes, the impact of type 2 diabetes on OSA incidence and the natural history of OSA have not been examined. It is plausible that type 2 diabetes could result in the development or worsening of pre-existing OSA. This might be related in part to the weight gain that occur in patients with type 2 diabetes with treatment intensification (particularly in the pre-incretin therapy era) and weight gain is a strong predictor of developing OSA or worsening of pre-existing OSA.<sup>27,28</sup> Other possible mechanisms include loss of upper airway innervations or the autonomic dysfunction that can occur in patients with type 2 diabetes, which is implicated in the central respiratory centre response to hypercapnic stimulus<sup>89</sup> and may result in changes in respiratory control resulting in sleep apnea.<sup>90</sup>

One study has examined the presence of witnessed sleep apneas (sleep reported) in 3,565 participants at baseline and after 6 years and found that HOMA-IR was an independent predictor of incident witnessed apneas (odds ratio [OR] 1.31 [1.13–1.51]) after adjustment for age, sex, and waist circumference.<sup>91</sup> Other independent predictors of witnessed sleep apneas included waist circumference (1.34 [95 % CI 1.19–1.52]), triglycerides (1.24 [1.09–1.41]), and smoking (1.52 [1.12–2.05])<sup>91</sup> – all of these factors might confer an increased risk for OSA in patients with type 2 diabetes.

**Table 1: Prospective Studies that Examined the Association between Obstructive Sleep Apnea and Incident Type 2 Diabetes**

Author(s)/ Study/Country	Population	Follow-up (Years)	Type 2 Diabetes Diagnosis	Results	Notes
Elmasry et al. <sup>*36</sup> 2000/Sweden	2,668 (all men, aged 30–69 years)	10	Questionnaire	Diabetes development: 5.4 % versus 2.4 % with versus without habitual snoring respectively (p<0.001). 13.5 % versus 8.6 % for obese snorers versus obese non-snorers, respectively (p=0.17). OR (95 % CI) 7.0 (2.9–16.9) versus 5.1 (2.7–9.5) for obese snorers versus obese non-snorers	Adjusted for: age, weight gain, smoking, alcohol dependence, and physical inactivity
Al-Delaimy et al. <sup>**37</sup> 2002/US	69,852 (all female nurses)	10	Self reported and questionnaire	Snoring was associated with risk for diabetes (occasional versus non-snoring, RR 1.48, 95 % CI 1.29–1.70; regular versus non-snoring, RR 2.25, 95 % CI 1.91–2.66)	Adjusted for: age and BMI
Reichmuth et al. <sup>§38</sup> 2005/US	1,387	4	FPG physician diagnosis	Adjusted OR for developing diabetes with an AHI of 15 or more: 1.62 (95 % CI 0.67–3.65)	Adjusted for: age, sex and body habitus
Marshall et al. <sup>§39</sup> 2009/Australia	295	4	Physician diagnosis or FPG	Moderate-severe OSA was an independent risk factor for incident diabetes (OR=13.45, 95 % CI 1.59–114.11)	Adjusted for: age, gender, waist circumference, BMI, BP, and HDL. Large 95 % CI due to small number of incident diabetes
Botros et al. <sup>§40</sup> 2009/US	544	2.7	Physician diagnosis and FPG	Adjusted HR per quartile of OSA severity=1.43 (95 % CI 1.10–1.86)	OSA defined as AHI ≥8. Adjusted for: age, sex, race, BMI, baseline fasting glucose, and weight change
Celen et al. <sup>§41</sup> 2010/Sweden	168 (from a sleep clinic)	16	Physician diagnosis	Incident type 2 diabetes: 15.5 % versus 24.6 % (p=0.02). OSA was a predictor of incident type 2 diabetes in women (OR 11.8, 95 % CI 1.1–121.7, p=0.04) but not men after adjustment	Adjusted for: age and BMI
Lindberg et al. <sup>**42</sup> 2012/Sweden	141 (all men)	11	OGTT	ODI >5 was a predictor of developing diabetes (adjusted OR 4.4, 95 % CI 1.1–18.1)	Adjusted for: age, BMI, change in BMI, hypertension, and CPAP treatment

Patients in these studies were free from type 2 diabetes at baseline. Obstructive sleep apnea (OSA) diagnosis based on \*questionnaire, \*\*overnight respiratory monitoring, §polysomnography. AHI = apnea-hypopnea index; BMI = body mass index; BP = blood pressure; CI = confidence interval; CPAP = continuous positive airway pressure; FPG = fasting plasma glucose; HDL = high-density lipoprotein cholesterol; HR = hazard ratio; ODI = oxygen desaturation index; OGTT = oral glucose tolerance test; OR = odds ratio; RR = risk ratio.

Future studies need to examine the natural history of sleep apnea (both obstructive and central) in patients with type 2 diabetes as this information will be important to develop the appropriate screening strategies for sleep apnea in patients with type 2 diabetes and to understand the metabolic and non-metabolic consequences of sleep apnea in patients with type 2 diabetes. The ongoing Sleep AHEAD study might provide some useful information about the natural history of OSA in patients with type 2 diabetes.

## Obstructive Sleep Apnea Prevalence in Patients with Type 2 Diabetes

Obesity is a major risk factor for OSA and type 2 diabetes and, as described above, OSA is an independent predictor of incident type 2 diabetes and is associated with IR and  $\beta$ -cell dysfunction. Hence, it is not surprising that several epidemiological studies showed that OSA is very common in patients with type 2 diabetes (8.5–85 %, 23.8–70 % for moderate to severe OSA).<sup>64,92–103</sup> Methodological and population differences account for the significant differences observed between studies in OSA prevalence. Studies with lower OSA prevalence tended to include a White European population and were conducted in primary care settings,<sup>94,102,103</sup> while studies of higher prevalence were conducted in secondary care settings or included Afro-Caribbeans.<sup>97,101</sup> Data regarding the prevalence of OSA in South Asians with type 2 diabetes is limited to one study that showed a higher prevalence in White Europeans compared with South Asians with type 2 diabetes, but the South Asians in this study had lower BMI and waist circumference than White Europeans.<sup>101</sup> As OSA is common in patients with type 2 diabetes, the International Diabetes Federation (IDF) recommended

screening for OSA in this high-risk population,<sup>104</sup> although the extent to which this recommendation is followed is to be determined and appropriate validated screening methods in patients with type 2 diabetes are still lacking. Whether the prevalence of OSA is higher in patients with type 2 diabetes compared with similar populations without type 2 diabetes remains unclear.

## Obstructive Sleep Apnea and Glycemic Control in Patients with Type 2 Diabetes

Due to its association with obesity, IR and  $\beta$ -cell dysfunction, it is plausible to speculate that OSA might worsen glycemic measures in patients with type 2 diabetes. However, as with most aspects of OSA-related research, obesity is a major confounder. Several studies of relatively small sample size (n=31–92) showed that OSA and OSA severity are associated with poorer glycemic control (both glycated hemoglobin [HbA<sub>1c</sub>] and fasting plasma glucose) and glycemic variability after adjustments for age, sex, race, BMI, number of diabetes medications, level of exercise, years of diabetes, and total sleep time in some studies.<sup>100,105–108</sup> The adjusted mean increase in HbA<sub>1c</sub> between patients with and without OSA varied between 0.7 to 3.69 % depending on the OSA severity. However, not all studies showed such an association;<sup>95</sup> however, in this study only 22 % of participants had full polysomnography and the duration of the sleep study was just 4 hours.<sup>109</sup> Another study showed no association between AHI and HbA<sub>1c</sub> in patients with type 2 diabetes after adjustment for confounders but there was an association between lowest oxygen saturation correlated with HbA<sub>1c</sub>.<sup>110</sup> Hence, most studies suggest a relationship between OSA

and glycemic measures in patients with type 2 diabetes, but some studies did not show such an association and causation is difficult to prove due to the cross-sectional nature of these studies, the confounding effects of obesity and the lack of prospective studies assessing the impact of OSA on HbA<sub>1c</sub> longitudinally.

To further add to the complexity, recent data suggest that the association between HbA<sub>1c</sub> and OSA in patients with type 2 diabetes is dependent on the sleep stage by showing that AHI is independently associated with HbA<sub>1c</sub> during REM but not during non-REM sleep.<sup>111</sup> The difference in HbA<sub>1c</sub> between the lowest and highest REM AHI quartile was about 1%.<sup>111</sup> This could explain some of the variability observed in previous studies as patients with similar total AHI might have different distributions of REM and non-REM AHI.

Several studies examined the impact of CPAP treatment on glycemic measures in patients with type 2 diabetes,<sup>76,92,112-117</sup> only one of which was randomized,<sup>76</sup> with the rest being uncontrolled pre-post assessments. The uncontrolled studies showed improvements in insulin sensitivity,<sup>92,112</sup> postprandial hyperglycemia,<sup>113</sup> glycemic variability,<sup>116</sup> and/or HbA<sub>1c</sub>.<sup>113,114</sup> The one randomized controlled trial showed no change in HbA<sub>1c</sub> after 3 months of CPAP therapy. The lack of a positive effect could be attributed to the small study sample, the limited duration of follow-up and the suboptimal adherence to CPAP (3.6 hours/night), or to a true lack of effect. A meta-analysis found that CPAP did not significantly reduce HbA<sub>1c</sub> (0.08% [95% CI -0.26 to 0.42]) in patients with type 2 diabetes.<sup>80</sup>

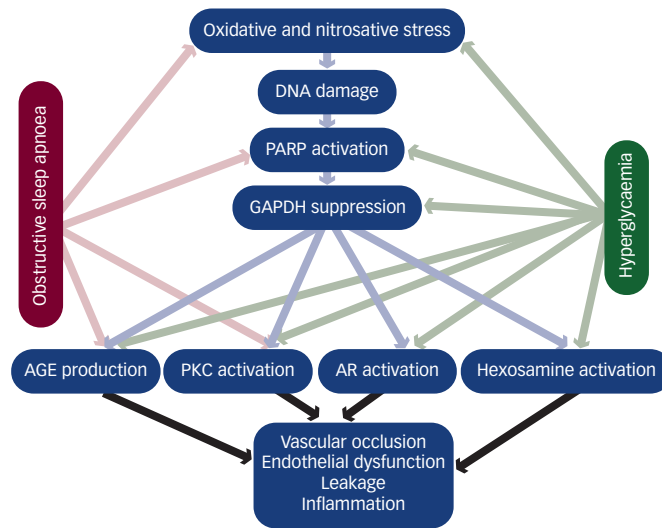
The association between REM AHI with HbA<sub>1c</sub>, rather than non REM AHI (described above), is another factor to be taken into account. Most of the REM sleep occurs towards the end of the night, hence longer usage of CPAP might be needed to produce an effect on glycemic measures. This was tested in a recent study presented in the SLEEP 2013 conference where patients with type 2 diabetes (mean BMI 39.2 kg/m<sup>2</sup>, diabetes duration 3.2 years), were randomized to 1 week in-laboratory (8 hours sleep) CPAP or sham CPAP to maximise CPAP adherence under direct supervision. CPAP resulted in a decrease of 11.2 and 19.8 mg/dl in the average 24-hour and post-breakfast glucose levels, respectively. The dawn phenomena was also reduced by 45%.<sup>118</sup> In addition to the better CPAP usage reported in this study, the diabetes duration was also relatively short, which might contribute to the CPAP effect.

Further randomized controlled trials are needed to assess the impact of CPAP on glycemic control in patients with type 2 diabetes; these trials might need to focus on better CPAP compliance, longer CPAP usage per night and possibly targeting patients with shorter diabetes duration. Another completed randomized trial (Effect of PAP Treatment on Glycemic Control in Patients With Type 2 Diabetes [GLYCOSA]) should report soon (<http://clinicaltrials.gov/ct2/show/study/NCT00509223?sect=X6015>).

### Obstructive Sleep Apnea and Hypertension in Patients with Type 2 Diabetes

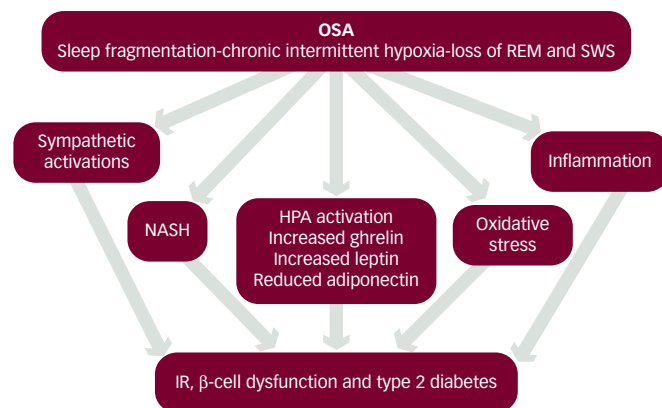
The links between OSA and arterial hypertension and the impact of CPAP treatment on BP in patients without diabetes are well established.<sup>119-124</sup> Emerging evidence suggests that the same might be true in patients with type 2 diabetes. In a retrospective cohort study in patients with OSA and

**Figure 3: Proposed Mechanisms Relating Obstructive Sleep Apnea to Microvascular Complications in Patients with Type 2 Diabetes**



The figure shows the possible mechanisms in which hyperglycemia can result in microvascular complications and the potential mechanisms in which obstructive sleep apnea (OSA) can contribute to the development of microvascular complications in diabetes. Both OSA and hyperglycemia share similar molecular mechanisms including oxidative stress, protein kinase C (PKC) activation and advanced glycation end product (AGE) production. Our own work has shown that patients with OSA and type 2 diabetes have increased oxidative and nitrosative stress and impaired microvascular complications compared with patients with type 2 diabetes only<sup>107</sup> and that patients with OSA and type 2 diabetes have poly ADP ribose polymerase (PARP) activation compared with patients without type 2 diabetes (unpublished data). AR = aldose reductase; GAPDH = glyceraldehyde 3-phosphate dehydrogenase.

**Figure 4: Possible Mechanistic Linking Obstructive Sleep Apnea to Dysglycemia**



HPA = hypothalamic-pituitary-adrenal axis; IR = insulin resistance; NASH = non-alcoholic steatohepatitis; OSA = obstructive sleep apnea; REM = rapid eye movement; SWS = slow-wave sleep.

type 2 diabetes, CPAP was associated with a mean change of -6.81 mmHg (95% CI -9.94 to -3.67 mmHg) and -3.69 mmHg (-5.53 to -1.85 mmHg) in systolic and diastolic BP, respectively, after nine to 12 months of treatment.<sup>125</sup> A randomized parallel group intervention trial showed similar results after 3 months of CPAP treatment.<sup>126</sup> Randomized placebo and active controlled studies are needed.

## Obstructive Sleep Apnea and Vascular Complications in Patients with Type 2 Diabetes

Macro and micro-vascular complications remain the major cause of morbidity and mortality in patients with type 2 diabetes. Several lines of evidence suggest increased risk for cardiovascular disease (CVD) in patients with OSA and observational studies suggest that CPAP treatment is associated with reduction in CVD.<sup>127–129</sup> In addition, in patients with stable coronary artery disease, AHI correlated positively with the plaque volume assessed by intravascular ultrasound ( $r=0.6$ ;  $p=0.01$ )<sup>130</sup> or computed tomography (CT) angiogram ( $r=0.4$ ;  $p=0.02$ ).<sup>131</sup> Furthermore, patients with OSA are more likely to develop acute myocardial infarction between 12 am and 6 am compared with non-OSA patients matched for comorbidities (32 % versus 7 %;  $p=0.01$ ) supporting the role of the nocturnal events that occur in OSA patients in the development of CVD.<sup>132</sup>

Data regarding the impact of OSA on CVD in patients with type 2 diabetes are limited. A cross-sectional analysis from the Look AHEAD study showed that AHI is associated with stroke (adjusted OR 2.57, 95 % CI 1.03–6.42), but there was no association with coronary artery disease,<sup>133</sup> but the CVD was self-reported. In a more recent study of 132 consecutive asymptomatic patients with type 2 diabetes and normal exercise echocardiographic findings for  $\leq 8$  years, sleep disordered breathing (SDB) was associated with incident coronary artery disease (adjusted hazard ratio [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;  $p < 0.01$ ) after a median follow-up of 4.9 years.<sup>134</sup>

Several studies examined the relationship between OSA and diabetes-related microvascular complications – most of these studies were cross-sectional in nature and interventional data are lacking. In Japanese patients undergoing vitreous surgery for advanced diabetic retinopathy (DR), lower oxygen saturations were associated with proliferative DR after adjustment for age, HbA<sub>1c</sub>, and hypertension.<sup>135</sup> 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 type 2 diabetes.<sup>136</sup> 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.<sup>137</sup> Longitudinally, patients with OSA were more likely to develop advanced 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 advanced DR compared with non-complaint patients.<sup>137</sup> In a proof of concept uncontrolled, hypothesis-generating study, CPAP treatment for 6 months was associated with improvement in visual acuity without an impact on macular edema/thickness.<sup>138</sup>

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 type 2 diabetes after adjustment for possible confounder.<sup>139</sup> After a 2.5-year follow-up of the same cohort, OSA was an independent predictor of study-end eGFR and eGFR decline.<sup>139</sup> In a study of Japanese patients with type 2 diabetes, ODI  $\geq 5$  was independently associated with microalbuminuria in women but not in men after adjustment for confounders.<sup>140</sup>

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.<sup>101</sup>

Several mechanisms might explain the observed associations between OSA and vascular disease in patients with type 2 diabetes. Hyperglycemia and OSA result in the activation of similar pathways (e.g. Aldose reductase, protein kinase C, advanced glycation end products) and increased oxidative and nitrosative stress that can lead to increased inflammation, cellular and endothelial dysfunction, and vascular disease (see *Figure 3*).<sup>141–162</sup> In recent studies, OSA was associated with increased oxidative stress, nitrosative stress, and impaired microvascular complications in patients with type 2 diabetes.<sup>101,139</sup>

## Obstructive Sleep Apnea and Type 2 Diabetes—The Mechanisms

The mechanisms underlying the relationship between OSA and type 2 diabetes are likely to be complex and multifactorial involving multiple neural and endocrine pathways (see *Figure 4*).

Intermittent hypoxia is an important component of OSA and contributes significantly to its pathologic consequences. Intermittent hypoxia for as little as 5 hours in healthy volunteers can reduce insulin sensitivity without a compensatory increase in insulin secretion, suggesting an impact on  $\beta$ -cell function as well.<sup>163</sup> The intermittent hypoxia and the repetitive episodes of re-oxygenation following desaturations that occur in OSA can simulate ischemia–reperfusion injury and result in the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) causing oxidative and nitrosative stress resulting in cellular and DNA damage and increased oxidised lipids, DNA and carbohydrates as shown in patients with OSA and animals exposed to intermittent hypoxia.<sup>101,144,146,161</sup> The impact of intermittent hypoxia on IR could be in part due to the hypoxia-inducible factor-1 (HIF-1) that is increased in OSA either secondary to hypoxia itself<sup>164</sup> or oxidative stress.<sup>165</sup> HIF-1 upregulates sterol regulatory element-binding protein (SREBP)-1,<sup>166</sup> which is associated with increased lipid biosynthesis and IR.<sup>167</sup> HIF is also involved in systemic inflammation.<sup>168</sup> Interestingly, in mice with partial deficiency of HIF-1, intermittent hypoxia does not result in IR.<sup>8,166</sup>

OSA is also associated with many hormonal changes that can affect glucose metabolism including activation of the hypothalamic–pituitary–adrenal (HPA) axis,<sup>169,170</sup> increased ghrelin,<sup>171</sup> and increased catecholamines secretion<sup>172</sup> all of which can be corrected with CPAP. OSA is also associated with changes in adipokine secretion including lower adiponectin levels,<sup>161,173,174</sup> and higher leptin levels.<sup>48,49</sup>

OSA is associated with increased sympathetic activity<sup>161</sup> that plays an important role in the regulation of glucose and fat metabolism and the development of type 2 diabetes.<sup>175</sup> Both recurrent hypoxia<sup>176</sup> and recurrent arousals<sup>177</sup> probably contribute to the activation of the sympathetic system.

In addition, OSA is associated with elevated inflammatory cytokines such as interleukin (IL)-6, tumor necrosis factor alpha (TNF- $\alpha$ ) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B),<sup>161</sup> which contributes to IR and  $\beta$ -cell dysfunction. In addition to intermittent hypoxia, OSA is associated with changes in sleep architecture such as reduction in SWS and sleep quality, which have been associated with reduction in insulin sensitivity and dysglycemia.<sup>178</sup>

OSA might also be a risk factor for the developing of histologically proven non-alcoholic fatty liver disease (NAFLD) and for progressing to NASH.<sup>61,179</sup> Nocturnal desaturations were found to be associated with hepatic inflammation, hepatocyte ballooning, and liver fibrosis.<sup>61</sup> Another study also found that subjects with histological NASH had significantly lower mean nocturnal oxygen saturation, and higher AHI compared with non-NASH controls.<sup>179</sup>

All the above-listed mechanisms can impact on IR and/or  $\beta$ -cell function resulting in impaired glucose metabolism and eventually type 2 diabetes.

## Summary and Conclusion

OSA is a common medical condition that is strongly linked to obesity. It is associated with increased IR and  $\beta$ -cell dysfunction and is a risk factor for the development of incident glucose intolerance/type 2 diabetes. Obesity remains a major confounder for the relationship between OSA and glycemic abnormalities but recent studies suggest that these associations hold true even in lean individuals with OSA. The mechanisms underlying this relationship between OSA and dysglycemia are complex and likely to involve several neural and endocrine mechanisms. OSA is common in patients with type 2 diabetes with most studies showing that more than half of patients with type 2 diabetes have some degree

of OSA. OSA is associated with worsening glycemic control in patients with type 2 diabetes and recent studies suggest that OSA is associated with increased macro- and microvascular complications and possibly hypertension in patients with type 2 diabetes. The mechanisms linking OSA to vascular disease in type 2 diabetes are likely to involve similar pathways to those stimulated by hyperglycemia in type 2 diabetes. The impact of CPAP treatment in patients with dysglycemia or type 2 diabetes remains controversial. While CPAP seems to improve IR, convincing evidence for the impact of CPAP on glycemic control in patients with type 2 diabetes is still lacking. Recent observational data suggest that CPAP might have a favorable impact on diabetes-related vascular complication but evidence from randomized controlled trials is awaited.

While most of the research in the field of OSA and glucose metabolism focussed on euglycemic individuals or patients with pre-diabetes, research into the impact of OSA in patients with type 2 diabetes is rapidly expanding and gaining momentum. Further research into the impact of mild OSA in patients with type 2 diabetes and randomized controlled trials into the efficacy of OSA treatments on diabetes-related outcomes are needed. In addition, more work needs to be carried out to understand the impact of type 2 diabetes on OSA. ■

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