Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea

Brian D. Kent[1], Walter T. McNicholas[2,3], Silke Ryan[2,3]

[1]Pulmonary and Sleep Disorders Unit, Guy's and St Thomas' Hospital, London, UK; [2]Pulmonary and Sleep Disorders Unit, St. Vincent's University Hospital, Dublin; Ireland; [3]School of Medicine and Medical Science, University College Dublin, Dublin, Ireland

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Correspondence to: Dr. Silke Ryan, MD, PhD. Department of Respiratory Medicine, St. Vincent's University Hospital, Elm Park, Dublin 4, Ireland. Email: silke.ryan@ucd.ie.

Abstract: Obstructive sleep apnoea (OSA) is a highly prevalent disorder, which conveys an increased risk of cardiovascular disease and death. Type 2 diabetes mellitus (T2DM), glucose intolerance and insulin resistance (IR) are common in subjects with OSA, but a shared intimate relationship with obesity makes discerning an independent link challenging. Nonetheless, mechanistic studies suggest that OSA could contribute to impaired glucose metabolism via the effects of sleep fragmentation, sympathetic excitation and intermittent hypoxia (IH) on pancreatic B-cell function, insulin sensitivity, and systemic inflammation. In particular, emerging data suggest that IH may have an important detrimental effect on adipose tissue function and inflammation. Similarly, data from population—and clinic-level studies suggest that OSA is independently related with the prevalence and incidence of T2DM and IR, and may also lead to worse glycaemic control in diabetics. However, the ability of continuous positive airway pressure (CPAP) therapy to make a meaningful impact on T2DM or IR remains uncertain. In this review we explore the available evidence linking OSA with IR, glucose intolerance and T2DM, and discuss potential pathobiological mechanisms by which sleep disordered breathing can affect metabolic health.

Keywords: Obstructive sleep apnoea (OSA); intermittent hypoxia (IH); insulin resistance (IR); diabetes mellitus; inflammation

Obstructive sleep apnoea (OSA) is a clinical syndrome characterized by repeated episodes of pharyngeal obstruction during sleep that lead to intermittent hypoxia (IH), sleep fragmentation and excessive daytime sleepiness. It is a highly prevalent disorder affecting about 14% of men and 5% of women and its prevalence is rapidly rising due to the strong association of OSA with obesity (1). The major health burden in OSA patients is an increased risk of cardiovascular diseases, such as systemic arterial hypertension, coronary artery disease, heart failure and stroke, an association which is corroborated by numerous large-scale epidemiological and prospective studies (2). Furthermore, there is increasing evidence of an independent association of OSA with metabolic dysfunction, and in particular with alterations in glucose metabolism. Subjects with OSA seem to be at greater risk of developing type 2 diabetes mellitus (T2DM), insulin resistance (IR) and metabolic syndrome (MetS), an association which seems to be at least in part irrespective of the degree of obesity. Indeed, OSA and obesity may exert synergistic negative effects on glucose metabolisms. However, studies in this field have yielded inconsistent results, and the impact of OSA treatment on glucose metabolism and metabolic dysfunction is also not clearly established.

In this article, we will review the current evidence evaluating potential links between OSA and T2DM, IR and

MetS, including the potential impact of continuous positive airway pressure (CPAP) treatment on these consequences. We will further discuss the possible mechanisms underlying metabolic dysfunction in OSA, which include several pathophysiological pathways triggered by the characteristic features of OSA, namely sleep disturbance and IH.

Clinical and epidemiological data

Association between obstructive sleep apnoea (OSA) and type 2 diabetes mellitus (T2DM)

OSA in diabetic cohorts

Given their shared relationship with obesity, a substantial burden of sleep disordered breathing in diabetic cohorts and a high prevalence of T2DM in OSA populations is perhaps to be expected. However, there is increasing evidence that the two disorders may have an independent link, one beyond a simple shared association with obesity. OSA is certainly highly prevalent in patients with T2DM. When 240 subjects attending British hospital- and community-based diabetes clinics underwent domiciliary overnight oximetry, with confirmatory cardio-respiratory sleep studies performed on those whose oximetry was suggestive of sleep disordered breathing, 23% were found to have OSA [defined as an oxygen desaturation index (ODI) >10/h] (3). An even greater prevalence of OSA was found among 305 obese American diabetics evaluated using home polysomnography (PSG). In this cohort, only 13.4% did not have sleep disordered breathing, with 22.6% classified as severe OSA (4). A key explanatory factor for the discrepancy between these two studies was the degree of obesity within their cohorts—subjects in the US-based Sleep-AHEAD study had a mean body mass index (BMI) of 36.1 kg/m^2, compared with 28.8 kg/m^2 in the English group.

Prevalence of T2DM in OSA cohorts

Diabetes is also over-represented in patients with OSA when compared with the general population (*Table 1*). The most useful data in this regard is derived from large community-based studies. In the Wisconsin sleep cohort study, physician-diagnosed T2DM was present in 1.5% of participants with an apnoea/hypopnea index (AHI) <5, but 7.8% with an AHI ≥15 (5). Similarly, 8.8% of men and 7.7% of women with an AHI <5 in the Sleep Heart Health Study had known T2DM, compared with 16.9% and 16.7% respectively of those with an AHI ≥30 (14). In a large Canadian sleep clinic cohort, 4.4% without OSA had an antecedent diagnosis of

diabetes, *vs.* 15.3% with severe OSA (6).

The increased prevalence of T2DM in patients with more severe OSA is not completely explained by traditional risk factors for metabolic disease. In a community-based analysis of 1,387 subjects of the Wisconsin Sleep Cohort, 23% of whom had an AHI ≥5, moderate-severe OSA was independently associated with prevalent physician-diagnosed T2DM, despite adjustment for age, gender, and body habitus [adjusted odds ratio (OR) =2.30; 95% CI, 1.28-4.11] (5). This relationship was still stronger in those with an AHI ≥30 (adjusted OR =3.48; 95% CI, 1.69-7.18). Among 2,149 patients referred to Canadian sleep clinics for diagnostic testing, severe OSA conferred an adjusted OR of 1.82 (95% CI, 1.07-3.10) for concomitant T2DM (6). In this study diabetes was defined according to self-report, physician diagnosis, medication usage, or from administrative database records. Perhaps surprisingly, this relationship appeared to be confined to sleepy subjects—those with an Epworth Sleepiness Score (ESS) score ≥10 had an adjusted OR of 2.59 (95% CI, 1.35-4.97) for prevalent diabetes, as compared with 1.16 (95% CI, 0.31-4.37) for those without subjective daytime sleepiness.

An important limitation of population-level studies of T2DM prevalence in sleep disordered breathing is their reliance on patient self-reporting, administrative databases or fasting plasma glucose measurement to establish a diagnosis of T2DM. The European Sleep Apnoea Cohort (ESADA) study is a multi-centre, multinational study involving over 15,000 patients attending sleep laboratories across Europe, Israel and Turkey. Participants in ESADA are screened at enrolment with glycosylated haemoglobin (HbA1c) measurement, which has recently been approved as a stand-alone diagnostic test for T2DM (15), and may identify a higher proportion of diabetics in sleep cohorts than reliance on fasting plasma glucose (16). In an analysis of nearly 7,000 subjects in the ESADA cohort, a diagnosis of severe sleep disordered breathing was associated with a markedly increased likelihood of prevalent T2DM, following adjustment for obesity, age, co-morbidities and medication use (adjusted OR =1.87; 95% CI, 1.45-2.42) (8).

Similarly, data from smaller, clinic-based studies using more robust methods to detect occult hyperglycaemia support an independent relationship between OSA and T2DM. In a French study of 595 men with suspected OSA undergoing PSG and subsequent oral glucose tolerance testing (OGTT), T2DM was found in 30.1% of subjects with an AHI >10, compared with 13.9% of non-apnoeic snorers (17). In a multivariate linear regression model, AHI

Table 1 Selected population studies population studies of associations between OSA and diabetes mellitus, glucose intolerance or insulin resistance

Authors	Participants	Study design	Outcome measures	Findings
OSA and type 2 diabetes mellitus				
Reichmuth *et al.* (5)	1,387 subjects community based	Observational	T2DM prevalence and incidence; T2DM defined by physician report or FPG	Increased prevalence of T2DM if AHI >15 (AOR 2.30); no increased incidence of T2DM with OSA after 4 years
Ronksley *et al.* (6)	2,149 subjects clinic based	Cross sectional	T2DM prevalence; T2DM defined by self-report and medication use	Independent association of severe OSA with T2DM (AOR 2.18); relationship confined to sleepy subjects
Botros *et al.* (7)	1,233 subjects clinic based	Observational	T2DM incidence	Increased incidence of T2DM with OSA (HR 1.43 per AHI quartile); CPAP use appeared to attenuate T2DM risk
Kent *et al.* (8)	6,616 subjects clinic based	Cross sectional	T2DM prevalence and control; T2DM defined by medication use, prior diagnosis or HbA1c ≥6.5%	Increased prevalence of T2DM with severe OSA (AOR 1.87); worse glycaemic control in diabetics with severe OSA
Kendzerska *et al.* (9)	8,678 subjects clinic based	Historical cohort	T2DM incidence; T2DM defined by related healthcare utilisation	Increased incidence of T2DM with severe OSA (HR 1.31)
OSA, insulin resistance and glucose intolerance				
Punjabi *et al.* (10)	2,656 subjects community based	Cross sectional	IGT measured by OGTT; IR estimated by HOMA-IR	Increased IGT with AHI >15 (AOR 1.46); elevated HOMA-IR with AHI >15 and increasing nocturnal hypoxaemia
Theorell-Haglow *et al.* (11)	400 female subjects community based	Cross sectional	Insulin sensitivity index derived from OGTT	Increasing AHI associated with reduced insulin sensitivity
Priou *et al.* (12)	1,599 subjects clinic based	Cross sectional	Pre-diabetes (HbA1c 6-6.49%)	Pre-diabetes more common with severe (AOR 2.02) or very severe OSA (AOR 2.96)
Kent *et al.* (13)	5,294 subjects clinic based	Cross sectional	Adjusted mean HbA1c levels by AHI quartile; pre-diabetes (HbA1c 6-6.49%)	Increasing HbA1c levels with increasing AHI; pre-diabetes more common in highest AHI quartile (AOR 2.12)

OSA, obstructive sleep apnoea; T2DM, type 2 diabetes mellitus; AHI, apnoea/hypopnea index; CPAP, continuous positive airway pressure; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance testing; HOMA-IR, homeostasis model assessment of insulin resistance.

was an independent negative predictor of insulin sensitivity. In a similar study, 129 Japanese patients with newly diagnosed OSA underwent OGTT; a post-load glucose in the diabetic range was found in 33.8% with an AHI ≥30 *vs.* 15% with an AHI <15 (18). In both of these studies, a large proportion of subjects had undiagnosed T2DM, emphasising the importance of rigorous screening in clinical and epidemiological studies.

Incidence of T2DM in OSA cohorts

There is some discordance in the published literature on how OSA may predict the subsequent development of T2DM. Studies evaluating snorers, performed largely without objective assessment of sleep-disordered breathing, are suggestive of a link. A questionnaire-based study of 2,504 Swedish men aged 30-69 assessed the relationship of self-reported snoring with development of self-reported T2DM over a 10-year period (19). The 2.4% of non-snorers developed T2DM over the study period, compared with 5.4% of snorers. In an analysis confined to obese participants, 13.5% of snorers and 8.6% of non-snorers reported incident T2DM. A complimentary study of 69,852 US

female nurses found regular snorers had an adjusted OR of 2.02 (95% CI, 1.71-2.40) for incident T2DM over a decade of follow-up compared with non-snorers, following adjustment for obesity, age and other risk factors for metabolic disease (20).

Few studies have longitudinally evaluated if objectively measured sleep disordered breathing constitutes an independent risk factor for T2DM. The 26 new cases of T2DM occurred among 978 participants in the Wisconsin sleep cohort over 4 years of follow-up, and in unadjusted analysis moderate-severe OSA was associated with an increased likelihood of incident diabetes mellitus (OR =4.06; 95% CI, 1.86-8.85) (5). This relationship was abolished following adjustment for age, gender, and body habitus (adjusted OR =1.62; 95% CI, 0.67-3.65; P=0.24), and no alteration in risk of T2DM was seen in those commenced on CPAP treatment. Conversely, in a study of 544 subjects referred for assessment of suspected sleep disordered breathing with a mean duration of follow-up of 2.7 years, T2DM occurred at a rate of 5.5 cases per 100 patient years in OSA patients, as opposed to 1.8 cases per 100 patient years in non-apnoeic snorers (7). This relationship survived adjustment for confounding variables [adjusted hazard ratio (HR) per AHI quartile =1.43; 95% CI, 1.10-1.86), and CPAP significantly attenuated the risk of incident T2DM (HR =0.53; 95% CI, 0.28-0.99).

Similarly, a recent historical cohort study, evaluating over 8,000 non-diabetic Canadian subjects attending a sleep laboratory, found that after a median follow-up period of 67 months, and following statistical adjustment for confounding factors, subjects with severe OSA were 30% more likely to develop clinically overt T2DM than those with an AHI <5 (9).

Glycaemic control in subjects with diabetes mellitus and obstructive sleep apnoea (OSA)

The presence of sleep disordered breathing may also contribute to poor diabetic control. In a study of 60 US patients recruited from a hospital diabetes clinic, 77% were found to have OSA (21). Increasing OSA severity was associated with increased HbA1c levels after adjustment for demographic, anthropometric and clinical variables, with an adjusted mean HbA1c level 3.69% higher among diabetics in the severe OSA group than in the non-apnoeic group. HbA1c also correlated significantly in multivariate linear regression analysis with AHI and other indices of sleep disordered breathing.

Among over 1,100 subjects with T2DM participating

in the ESADA study, increasing OSA severity predicted increased likelihood of suboptimal glycaemic control (HbA1c >7%) (22). When compared with non-apnoeic diabetic patients, those with severe OSA had an adjusted OR of 2.02 (95% CI, 1.11-3.66) for poor diabetic control, following adjustment for confounding factors including prescription of diabetic medications (8). Similarly, adjusted mean HbA1c levels among diabetic patients increased with increasing OSA severity, from 6.76% (95% CI, 6.39-7.13) in those with no OSA to 7.48% (95% CI, 7.18-7.79) in those with severe OSA.

Treatment of obstructive sleep apnoea (OSA) and glycaemic control

The ability of CPAP therapy to make a meaningful impact upon diabetic control remains unclear (*Table 2*). Insulin sensitivity, as measured by hyperinsulinaemic euglycaemic clamp, improved significantly from 11.4±6.2 to 15.1±4.6 µmol/kg/min in 10 Australian diabetic subjects with significant OSA after 4 months CPAP (31). In another small study of 9 German diabetics, 3 months of CPAP improved insulin sensitivity, but had no significant impact upon HbA1c levels (32). A novel study of 20 diabetics with newly diagnosed OSA (AHI >15) evaluated nocturnal interstitial glucose measurements before and after 3 weeks of CPAP therapy, finding a significant decrease with CPAP [from (122.0±61.7) to (102.9±39.4) mg/dL; P=0.03] despite many of the participants gaining weight between the two studies (33). Unsurprisingly given the short duration of this study, no change was seen in HbA1c levels.

Conflicting results were produced by two of the more robust studies in this area. Babu *et al.* evaluated 25 obese diabetic subjects with OSA who were naïve to CPAP treatment (24). HbA1c levels and fasting interstitial glucose were measured before and after an average of 83 days of CPAP use. No significant change was observed in HbA1c levels in the overall cohort, but analyses restricted to subjects with a baseline HbA1c ≥7% or those with objective CPAP usage >4 h/night showed a reduction in HbA1c measurements. Furthermore, the improvement in glycaemic control correlated significantly with the number of nights of CPAP use (r=0.74; P=0.006). In the only randomised controlled trial specifically assessing the influence of CPAP therapy on diabetic control, 42 men with known T2DM and newly diagnosed OSA (ODI >10) were given therapeutic or sham CPAP for 3 months (23). As expected, those in the treatment group had improvements in daytime sleepiness and maintenance of wakefulness test results. However,

Table 2 Selected studies examining the effect of CPAP on diabetes, glucose intolerance and insulin resistance (IR)

Authors	Participants	Study design	Outcome measures	Findings
West et al. (23)	42 diabetic men, 4% ODI >10	RCT: CPAP vs. Sham (3 months)	Insulin resistance; HbA1c levels	No significant improvement with therapeutic CPAP
Babu et al. (24)	25 diabetics with OSA	Observational: median 83 days CPAP	Continuous glucose monitoring; HbA1c levels	Improved post-prandial glucose levels post-CPAP; improved HbA1c in subjects with baseline HbA1c >7%
Barcelo et al. (25)	44 diabetics with OSA	Observational: 3 months CPAP	Insulin levels; HOMA-IR	Reduced insulin resistance with CPAP in sleepy subjects only
Hoyos et al. (26)	65 non-diabetics, AHI >20	RCT: CPAP vs. Sham (12 weeks)	Insulin sensitivity; HOMA-IR	No significant improvement with therapeutic CPAP
Lam et al. (27)	61 men, FPG <6.1, AHI >15	RCT: CPAP vs. Sham (1 week)	Insulin sensitivity	Improved insulin sensitivity with CPAP; changes not maintained at 12-week follow-up, except in overweight subjects
Weinstock et al. (28)	50 subjects, AHI >15, impaired glucose tolerance	Crossover RCT: CPAP vs. Sham (8 weeks)	Resolution of IGT on OGTT; insulin sensitivity	No difference in likelihood of achieving normal OGTT; CPAP improved insulin sensitivity in subjects with AHI >30
Coughlin et al. (29)	34 non-diabetic subjects, mean RDI 40	Crossover RCT: CPAP vs. Sham (6 weeks)	HOMA-IR; resolution of metabolic syndrome	No significant difference in IR, strong trend in favour of CPAP; no difference in overall metabolic syndrome
Harsch et al. (30)	40 non-diabetic subjects, mean AHI 43	Observational: CPAP (3 months)	Insulin sensitivity	Improved insulin sensitivity after 2 days, maintained at 3 months; more significant improvement if BMI <30

CPAP, continuous positive airway pressure; ODI, oxygen desaturation index; RCT, randomised-controlled trial; OSA, obstructive sleep apnoea; HOMA-IR, homeostasis model assessment of insulin resistance; AHI, apnoea/hypopnea index; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance testing; RDI, respiratory disturbance index.

no improvements in HbA1c levels or measures of insulin sensitivity were observed. Overall CPAP compliance in the treatment arm was sub-optimal (average nightly use 3.6 h), but even with the exclusion of those who were particularly non-compliant, there was no benefit seen in glycaemic control with CPAP. Hence, it remains unproven if CPAP can act as an adjunct in diabetes control in diabetic subjects with sleep disordered breathing.

Association between obstructive sleep apnoea (OSA), insulin resistance (IR) and glucose intolerance

Insulin resistance (IR), glucose intolerance and obstructive sleep apnoea (OSA)

IR among non-diabetic subjects is associated with subsequent increased risk of T2DM and cardiovascular morbidity, and is an independent predictor of overall and cardiac mortality (34). Attempts to evaluate the relationship of OSA with IR are again complicated by the pivotal role played by obesity in driving these disorders, but an expanding evidence base is supportive of the existence of an independent link.

Clinic-based and case control studies from North America, Asia and Europe have suggested that the presence and severity of OSA is independently associated with IR. Among 270 non-diabetic subjects attending a Hong Kong sleep clinic, 68.5% of whom had an AHI ≥5, homeostasis model assessment of insulin resistance (HOMA-IR) was higher in those with OSA and increased with increasing OSA severity (35). This relationship survived adjustment for confounding factors, and was observed in both obese and non-obese subjects. Punjabi et al. studied 150 middle-aged, overweight or mildly obese men, who were free of known cardiometabolic disease (36). An AHI ≥5 was associated with an increased risk of glucose intolerance (OR =2.15; 95% CI, 1.05-4.38) independently of the effect of obesity.

Data focusing on morbidly obese subjects and women have shown similar relationships. Severity of sleep

disordered breathing predicted an elevated HOMA-IR in 90 patients recruited from a bariatric clinic (37), while increasing OSA severity was associated with decreased insulin sensitivity in a cohort of 400 non-diabetic Swedish women (11). In the majority of these studies, measures of nocturnal hypoxaemia had the most robust relationship with impaired glycaemic health, suggesting a potential pathophysiological role of IH. Underscoring this, data from 394 participants in the Cleveland Family Study showed the overall burden of nocturnal hypoxaemia (expressed as the cumulative sleep time with SpO_2 <90%) to be the key predictor of impaired glucose tolerance (IGT) in OSA patients (38).

There are limited population-level data in this area (*Table 1*). In a community-based North American study of 2,656 subjects, 8.7% with a respiratory disturbance index (RDI) <5 had IGT on fasting plasma glucose measurement *vs.* 17.5% with an RDI ≥15, a relationship which persisted after statistical adjustment for confounding variables (adjusted OR =1.46; 95% CI, 1.09-1.97) (10). In an evaluation of the relationship of HbA1c levels with indices of OSA severity in 1,599 subjects without diabetes attending French sleep laboratories (12), multivariate regression analysis showed an association between increased HbA1c levels and OSA severity, most marked in patients with an AHI ≥50 (adjusted OR =2.96; 95% CI, 1.58-5.54). Most recently, a similar analysis of 5,294 non-diabetic participants in the pan-European ESADA study, showed a dose dependent relationship between glycaemic health and severity of sleep disordered breathing, with a significantly higher adjusted HbA1c level in highest AHI quartile (5.50%; 95% CI, 5.46-5.53%) than in the lowest (5.24%; 95% CI, 5.21-5.27%) (13).

Treatment of obstructive sleep apnoea (OSA) and insulin resistance (IR)

The effect of CPAP therapy on insulin sensitivity in non-diabetic subjects remains controversial, with uncontrolled studies suggesting some benefit, but randomised trials providing much more uncertain data (*Table 2*). Insulin sensitivity improved with two nights of nocturnal CPAP in 40 treatment-naïve, non-diabetic German subjects (30). This effect was maintained at 3 months, but appeared to be largely confined to non-obese patients. A Spanish study of 44 men with newly diagnosed OSA also found treatment with CPAP to be associated with reductions in HOMA-IR and insulin levels, but only in subjects with objective daytime sleepiness at baseline (25).

A randomised, double-blind, crossover trial enrolled 35 British patients free of diabetes, including subjects with known IR (29). Six weeks of CPAP lowered HOMA-IR to a greater degree than sham CPAP, but the difference did not reach statistical significance (Δ=−0.6; 95% CI, −1.3-0.1; P=0.08), whereas daytime sleepiness and blood pressure improved significantly with treatment. Meanwhile, a study of 61 Chinese subjects with an AHI ≥15 randomised to therapeutic vs. sham CPAP for 1 week found insulin sensitivity improved significantly in the treatment group (27). However, a longer term follow-up of the patients who received therapeutic CPAP found no significant change from baseline insulin sensitivity at 3 months, and the authors excluded all subjects with known IR, making its applicability to other OSA cohorts uncertain. Similarly, data from the United States and Australia suggest that CPAP may only have a beneficial effect on glucose tolerance in individuals with severe OSA (28), or on insulin sensitivity after prolonged utilisation (26), respectively.

A number of recent meta-analyses have assessed the effect of CPAP therapy on IR in non-diabetic patients with OSA. These analyses included both uncontrolled studies and randomised-controlled trials (RCTs), but overall did suggest some reduction in HOMA-IR with medium-term use of CPAP, at least amongst compliant patients (39,40). However, there is a clear need for large, well-designed RCTs in this area.

Obstructive sleep apnoea (OSA) and metabolic syndrome (MetS)

While a number of competing, more precise definitions exist (41,42), the MetS is broadly composed of coexistent IR, hypertension, abdominal obesity and dyslipidaemia, and is associated with increased cardiovascular mortality (43). MetS is highly prevalent in OSA cohorts (44), occurring in up to 87% of OSA patients in some series (45). Once again, the confounding effect of visceral adiposity has made it difficult to definitively identify an independent relationship between the two conditions.

There are only a limited number of well-conducted studies examining the effect of CPAP therapy on MetS as an entity. When 34 British subjects with moderate-severe OSA were commenced on 6 weeks of CPAP in a sham-controlled, cross-over fashion, daytime sleepiness and BP improved on CPAP, but the overall prevalence of MetS did not (29). Similarly, in a secondary analysis of a study involving 65 men randomised to therapeutic or sham CPAP for

12 weeks, no significant differences were observed between the two groups in regression or development of MetS (46). A number of uncontrolled studies have suggested that CPAP may be beneficial in this context (47), and CPAP certainly can improve individual component factors of MetS, particularly hypertension (48). However, there is a need for large, prospective RCTs in this field.

In summary, OSA is associated with increased likelihood of T2DM, IR and MetS, and diabetic subjects with severe OSA appear to be less likely to achieve adequate glycaemic control. However, it remains to be established if CPAP therapy can improve metabolic health in pre-diabetic or diabetic subjects.

Potential mechanisms of glucose metabolic dysregulation in obstructive sleep apnoea (OSA)

The pathophysiological mechanisms of alterations in glucose metabolism in OSA are incompletely understood. The process is likely multifactorial and our current concept involves sympathetic nervous system overactivity, systemic and adipose inflammation, oxidative stress and hormonal alterations among the most important pathways. Although the evidence for a causal link remains limited, the major characteristics of OSA, namely sleep fragmentation/deprivation and IH, likely play pivotal roles as triggering factors of the pathophysiology.

Sleep fragmentation/deprivation and glucose metabolic dysfunction

Sleep fragmentation and reduction in total sleep time are characteristic features of OSA. Although this subject is poorly investigated directly in OSA cohorts, one could extrapolate data on sleep fragmentation and reduction in other settings. There is a stream of laboratory and epidemiological data showing an association of these features with T2DM and IR. Several cross-sectional and longitudinal studies, mainly using self-reported sleep duration, suggest that short sleep duration (generally defined as less than 6 h of sleep) is associated with increased risk of T2DM (49-54). In a recent meta-analysis, the relative risk (RR) for the development of T2DM with short sleep was estimated as 1.28 (55). In experimental studies, restricting sleep duration in healthy young subjects leads to alteration in glucose metabolism indicated by a decrease in insulin sensitivity, with subsequent reduced glucose tolerance (56-58).

Independently of reductions in sleep duration, sleep fragmentation with suppression of slow wave sleep also results in impaired insulin sensitivity without compensatory increase in insulin release, as demonstrated in a recent study on healthy volunteers (59). In addition, prospective population-based studies have shown an association between self-reported poor sleep quality and incident T2DM (53,60-62).

The mechanisms by which sleep deprivation and fragmentation contribute to alterations in glucose metabolism are incompletely understood. Sleep deprivation has been found to induce a pro-inflammatory state, with an increase in the release of interleukin (IL)-6 and tumour necrosis factor (TNF)-α and decreased adiponectin levels (63-66)—alterations which have been linked to IR (67). However, negative findings have also been reported, possibly due to considerable variability in baseline levels of these markers and normal circadian fluctuations (68-70). Gender differences have also been observed, and some studies have suggested that sleep restriction was associated with elevation in pro-inflammatory markers in men but not in women (66).

There is also compelling evidence for a role of sympathetic activation—which negatively affects insulin secretion and sensitivity (71,72)—in response to sleep deprivation and fragmentation, reflected in an increase in blood pressure, lower heart rate variability and decreased baroreflex sensitivity (58,73). Some studies also reported increased catecholamine concentration following sleep deprivation (56,57,69). Disturbances in the secretory profiles of the hormones cortisol and growth hormone (GH) may also contribute to the pathogenesis. Cortisol inhibits insulin secretion and elevations of cortisol in response to sleep deprivation and fragmentation have been detected in various studies (56,58,74-76). GH inhibits insulin activity, and usually peaks in the first half of the sleep period. Sleep restriction appears to be associated with a longer elevation of GH secretion during the night, and also a large secretory burst before sleep onset, leading to adverse effects on glucose regulation (77,78).

Several short-term laboratory studies support the assumption that short sleep alters the hormonal regulation of food intake by increasing levels of the appetite-stimulant hormone ghrelin, and by reducing levels of the suppressor leptin, leading to the subjective feeling of hunger with consequent increased caloric intake (79). Furthermore, there is evidence that daytime sleepiness and fatigue as a result of insufficient sleep may lead to reduction in physical activity and subsequent energy expenditure (80).

Collectively, sleep deprivation and fragmentation may contribute to metabolic dysfunction in OSA by various mechanisms. The direct relationships of these pathophysiological triggers in OSA populations, however, remain unknown, and there is a distinct lack of well-designed studies investigating this area.

Intermittent hypoxia (IH) and glucose metabolic dysfunction

IH, characterized by short repetitive cycles of desaturation followed by rapid reoxygenation, is the hallmark feature of OSA and is increasingly recognized as the major pathophysiological trigger for cardiovascular and metabolic disease processes associated with the disease (81). Cell culture and animal models have been developed, allowing the study of IH as a single component of the disease, precisely controlling the triggering events, both in severity and duration and thus, *in vitro* and animal studies have greatly contributed to our current knowledge. In lean and obese mice, chronic IH exposure contributes to decreased insulin sensitivity, an effect which is partially reversible after cessation of the stimulus (82-85). IH may affect glucose metabolism through systemic effects, including sympathetic excitation, inflammation or oxidative stress and through direct effects on adipose tissue, liver and pancreas.

Intermittent hypoxia (IH), sympathetic activation, systemic inflammation and oxidative stress

IH has been demonstrated to trigger multiple pathways potentially involved in the pathogenesis of cardiovascular and metabolic diseases (81). Sympathetic excitation in response to IH has been extensively studied in humans and rodents, and is widely believed to contribute to arterial systemic hypertension and other cardiovascular consequences (86). In addition, catecholamines are known to decrease insulin sensitivity and to reduce insulin-mediated glucose uptake (71,72). Several studies have demonstrated increased blood pressure and an associated rise in sympathetic activity in OSA patients versus matched controls, with improvement following short-term CPAP therapy (87-90). IH rodent models reproduce these changes, with blood pressure increases due to IH preventable by pharmacological and surgical blockage of the sympathetic nervous system (91,92). A recent study investigated the effect of adrenal medullectomy on glucose metabolism in mice treated with IH, and although surgery led to improved insulin secretion, IH-induced hyperglycaemia and IR remained unaffected, supporting the need for further

studies on this subject (93).

OSA-related IH has generally been associated with increased production of reactive oxygen species (ROS) and thus is thought to promote oxidative stress, which may contribute to alteration in glucose metabolism (94). Nonetheless, supporting data are sparse and results have been inconsistent. Jelic *et al.* harvested venous endothelial cells from OSA patients and matched controls, detecting higher levels of the oxidative stress marker nitrotyrosine in OSA subjects, with a significant fall following CPAP therapy (95). Studies in rats have demonstrated that IH leads to increased lipid peroxidation which correlated with left ventricular dysfunction (96). However, large studies have failed to show a beneficial effect of antioxidant therapy on cardiovascular diseases, and oxidative stress could potentially be a consequence rather than a cause of vascular inflammation and subsequent atherosclerosis (97).

Vascular and systemic inflammation are central in the pathogenesis of OSA-associated cardiometabolic processes and there is overwhelming support from human and animals studies of the key role of IH in driving inflammatory responses (98-100). IH activates the transcription factor nuclear factor-kappa B (NF-κB) (101-103). NF-κB is the master regulator of an inflammatory response, and numerous inflammatory, pro-atherogenic genes, such as TNF-α, IL-8 or intercellular adhesion molecule 1 (ICAM-1), are under its control. NF-κB activation has been demonstrated in cardiovascular tissue from mice treated with IH, and in cultured monocytes from OSA patients (101,103). Using a cell culture model of IH, our group demonstrated a preferential activation of NF-κB-dependent pro-inflammatory pathways by IH over adaptive, hypoxia-inducible factor 1 (HIF-1) mediated pathways, which is in contrast to sustained hypoxia where adaptive pathways predominate (102). Systemic and vascular levels of NF-κB-dependent pro-inflammatory mediators have been found to be increased in OSA patients *vs.* controls, potentially contributing to endothelial dysfunction, and CPAP therapy has a beneficial effect on these effects (100,104,105).

Effect of IH on adipose tissue

There is increasing evidence for an interaction between OSA and obesity in the development of cardiovascular and metabolic diseases. Obesity is strongly associated with OSA—the prevalence of OSA in obese subjects exceeds 30% and at least 60% of OSA patients are obese (106). Obesity exerts many of its cardiovascular and metabolic complications through the action of the white adipose tissue (WAT). WAT has been identified as a highly active endocrine

organ secreting multiple proteins—termed adipokines—which contribute to many pathophysiological processes (107). Metabolically dysfunctional adipose tissue is characterized by infiltration of macrophages and other immune cells including T-lymphocytes and mast cells. In addition, macrophages associated with obesity are polarized to a M1 or "classically activated" phenotype, and these M1 macrophages produce pro-inflammatory cytokines such as IL-6 and TNF-α, express inducible nitric oxide synthase (iNOS) and promote obesity-induced IR. In contrast, in lean subjects macrophages predominantly show an alternative, M2-pattern of expression with upregulation of anti-inflammatory factors such as IL-10 or adiponectin, and downregulation of pro-inflammatory cytokines, and thus are associated with tissue repair and resolution of inflammation (108).

There is emerging evidence that in obesity, where there is excess of adipose tissue, hypoxia is a key factor in modulating the pro-inflammatory response of WAT (109). As IH represents a stronger inflammatory stimulus than sustained hypoxia, this process may be potentiated by IH associated with OSA. Various studies have demonstrated that WAT in obese humans or rodents is more hypoxic than in lean controls (110,111). Given the technical difficulties in the direct measurement of rapid fluctuations in oxygen concentrations in tissue there are currently no data on the potential additive effect of IH in OSA subjects. Reinke et al. investigated the oxygen profile in response to IH in a mouse model and suggested that the oxygen fluctuations of IH are attenuated in adipose tissue (112). It is unknown, however, how this potentially relates to human adiposity and it is likely that there will be significant local differences within tissue depending on the relative distance to the circulatory system.

The master transcriptional regulator in response to hypoxia is HIF-1, which regulates transcription of numerous genes affecting various processes such as angiogenesis, metabolism, vascular tone and cell survival (113). It has recently been shown that HIF-1 activation occurs at the onset of obesity as a response to relative tissue hypoxia leading to adipose tissue inflammation and metabolic dysfunction (114); importantly genetic or pharmacological inhibition of HIF-1 proved protective in this setting. Meanwhile, hypoxia has previously been shown to inhibit insulin signalling and glucose transport in human and murine adipocytes in a HIF-1 dependent manner (115). Adipose HIF-1 activation in response to IH has also been recently demonstrated in ApoE-deficient lean mice, and this event was associated with accelerated atherosclerosis (116). Using the same

mouse strain, the hypoxia research group of the University of Grenoble, France, recently demonstrated increased macrophage infiltration of adipose tissue and increased expression of monocyte chemoattractant protein (MCP)-1, abnormalities which were associated with reduced insulin sensitivity and more advanced atherosclerotic lesions (117). However, in morbidly obese patients, IH does not appear to worsen macrophage accumulation in omental and subcutaneous fat depots (118), but there are no data outside the morbidly obese population. In support of a mechanistic link between IH and adipose tissue, Gharib et al. identified a profound effect of IH on gene expression in WAT mapping to numerous processes, including metabolism and oxidative stress responses (119). As a potential explanation, primary human adipocytes exposed to IH in vitro are significantly more sensitive to this pro-inflammatory stimulus than other primary cells, with the downstream consequence of increased activation of the NF-κB pathway and resultant expression of multiple inflammatory mediators known to play key roles in glucose metabolic dysfunction (120).

In summary, rapidly increasing evidence points to an additive effect of IH on adipose tissue inflammation, but further translational studies are urgently required to determine its detailed role.

Effect of IH on liver damage

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease characterized by the presence of ectopic fat in the liver, steatosis, which cannot be explained by alcohol consumption. It ranges from simple steatosis to non-alcoholic steatohepatits (NASH), that can progress to liver cirrhosis and is associated with the development of hepatocellular carcinoma (121). NAFLD is strongly associated with obesity, IR/T2DM and MetS (122). The relationship of NAFLD and IR is bi-directional, suggesting a self-perpetuating vicious cycle. Aron-Wisnewsky et al. systematically studied liver histology and overnight oximetry in morbidly obese patients undergoing bariatric surgery, and detected that the severity of IH—as indicated by the ODI—was associated with more severe liver injury, consistent with results of previous studies on OSA populations (118). Animal studies strongly support the detrimental role of IH on NAFLD progression, particularly evident in obese mice (82,123). The mechanisms underlying IH as "second hit" stimulus for NAFLD progression are largely unexplored and warrant further detailed studies. Furthermore, the role of CPAP therapy in potentially preventing NAFLD progression will need to be determined.
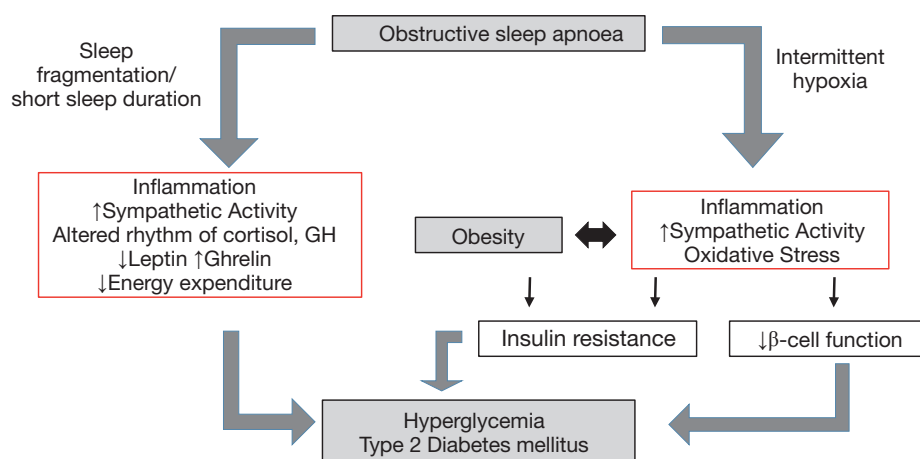
Figure 1 Potential mechanisms of alteration in glucose metabolism in obstructive sleep apnoea (OSA). GH, growth hormone.

Effect of IH on pancreatic B-cell function

B-cell dysfunction in response to IH is suspected based on the frequent observation that decreases in insulin sensitivity are often not matched by compensatory increase in insulin secretion. Louis *et al.* exposed a group of healthy volunteers to 8 h of IH or intermittent air in a randomized crossover design study, and despite worsening insulin sensitivity with IH, pancreatic insulin secretion was similar between both treatments (124). These results have subsequently been reproduced in mice and rats exposed to IH (83,84,125,126) and as a potential explanation, Polak *et al.* detected increased protein levels of the oxidative stress marker thiobarbituric acid reactive substances in pancreas isolated from mice treated with IH *vs.* intermittent air (84). The detailed mechanisms including the role of oxidative stress in this process, nonetheless, warrant further detailed investigation.

Conclusions and future directions

Evidence for an association of OSA and glucose metabolic dysfunction is rapidly growing. However, much of this evidence is derived from cross-sectional analyses and there is a clear need for large, well-designed, prospective studies. The lack of benefit with CPAP therapy in numerous studies demands a greater insight into the interaction of OSA and other contributing factors, in particular obesity, in the pathogenesis of alterations in glucose metabolism. IH and sleep deprivation/fragmentation likely play pivotal roles in the pathogenesis of glucose metabolic dysfunction in OSA, potentially contributing to multiple pathways likely synergistically with obesity (*Figure 1*). To further define

the mechanisms underlying these processes, clinical and translational studies are urgently required.

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Footnote

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