Obstructive sleep apnoea and type 2 diabetes mellitus: a bidirectional association

R Nisha Aurora, Naresh M Punjabi

Obstructive sleep apnoea and type 2 diabetes are common medical disorders that have important clinical, epidemiological, and public health implications. Research done in the past two decades indicates that obstructive sleep apnoea, through the effects of intermittent hypoxaemia and sleep fragmentation, could contribute independently to the development of insulin resistance, glucose intolerance, and type 2 diabetes. Conversely, type 2 diabetes might increase predisposition to, or accelerate progression of, obstructive and central sleep apnoea, possibly through the development of peripheral neuropathy and abnormalities of ventilatory and upper airway neural control. Although more research is needed to clarify the mechanisms underlying the bidirectional association between the two disorders, their frequent coexistence should prompt all health-care professionals to embrace clinical practices that include screening of a patient presenting with one disorder for the other. Early identification of obstructive sleep apnoea in patients with metabolic dysfunction, including type 2 diabetes, and assessment for metabolic abnormalities in those with obstructive sleep apnoea could reduce cardiovascular disease risk and improve the quality of life of patients with these chronic diseases.

Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, USA
(R N Aurora MD, Prof N M Punjabi MD)

Correspondence to:
Prof Naresh M Punjabi, Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA
npunjabi@jhmi.edu

The obesity epidemic has triggered an increase in the prevalence of many adverse health outcomes, ranging from cardiovascular disease to cancer.[1,2] Especially notable on the extensive list of obesity-related complications are both type 2 diabetes mellitus and obstructive sleep apnoea. Although obesity is a major risk factor for both disorders, evidence gathered during the past two decades has shown an independent association between the two—an association that persists even after the effects of obesity have been taken into account. Poor quality and low quantity of sleep is also being increasingly recognised as a potential cause of glucose intolerance, insulin resistance, and diabetes.[3–6] Furthermore, some evidence suggests that diabetes might increase the predisposition for obstructive sleep apnoea. Individually, both obstructive sleep apnoea and diabetes are highly prevalent disorders and are associated with adverse clinical sequelae that pose a substantial burden to public health. Combined, the negative effect of each disorder on health and society is multiplicative. The aim of this Review is to appraise the existing knowledge about the association between obstructive sleep apnoea and diabetes. The potential effect of obstructive sleep apnoea on glucose homoeostasis will be reviewed first, followed by an assessment of whether diabetes changes the development and progression of obstructive sleep apnoea. Thus, a major focus of this article is the bidirectional nature of the association between the two disorders.

Definitions

Sleep-disordered breathing

The term sleep-disordered breathing encompasses sleep-related breathing abnormalities that are characterised by the occurrence of apnoeas (complete cessation of airflow) and hypopnoeas (decrease in airflow) during sleep. Disordered breathing events are classified further into obstructive, central, and mixed events (figure 1). The classification of an event is dependent on evidence that the respiratory effort persists in the absence of airflow. An obstructive event is defined as no airflow despite continued respiratory effort. By contrast, a central event is defined as the absence of airflow with no associated respiratory effort. Cheyne–Stokes respiration is a disorder characterised by recurrent central events during sleep and a waxing and waning or crescendo-decrescendo pattern of tidal volume. Finally, a mixed event will typically start with a period that meets the criteria for a central event but will end with increasing respiratory effort. The number of events (apnoeas and hypopnoeas) per hour of sleep—the apnoea–hypopnoea index (AHI)—is used as a disease-defining metric for obstructive and central sleep apnoea. By clinical convention, the following thresholds are used to classify the severity of sleep apnoea: normal (AHI <5 events/h), mild (AHI 5·0–14·9 events/h), moderate (AHI 15·0–29·9 events/h), and severe (AHI >30 events/h).

Disorders of glucose metabolism

The American Diabetes Association recognises several categories of glycaemic status.[7] Type 1 diabetes mellitus accounts for 5–10% of all diabetes cases and results from autoimmune destruction of the pancreatic β cells. Type 2 diabetes mellitus accounts for 90–95% of all diabetes cases and results from a deficit in both insulin sensitivity and insulin secretion. The third category of diabetes mellitus encompasses a range of disorders that includes genetic defects of pancreatic β cells or of insulin action, endocrinopathies, drug-induced or chemical-induced pancreatic injury, infections, and other rare forms of immune-mediated diabetes. The fourth category is gestational diabetes mellitus, which is defined as glucose intolerance that develops during pregnancy. The diagnostic criteria for diabetes are as follows: symptoms of polyuria, polydipsia, or weight loss, and non-fasting blood glucose concentration ≥200 mg/dL (≥11·1 mmol/L); a fasting glucose concentration ≥126 mg/dL; or a 2-h post-challenge glucose concentration ≥200 mg/dL during an
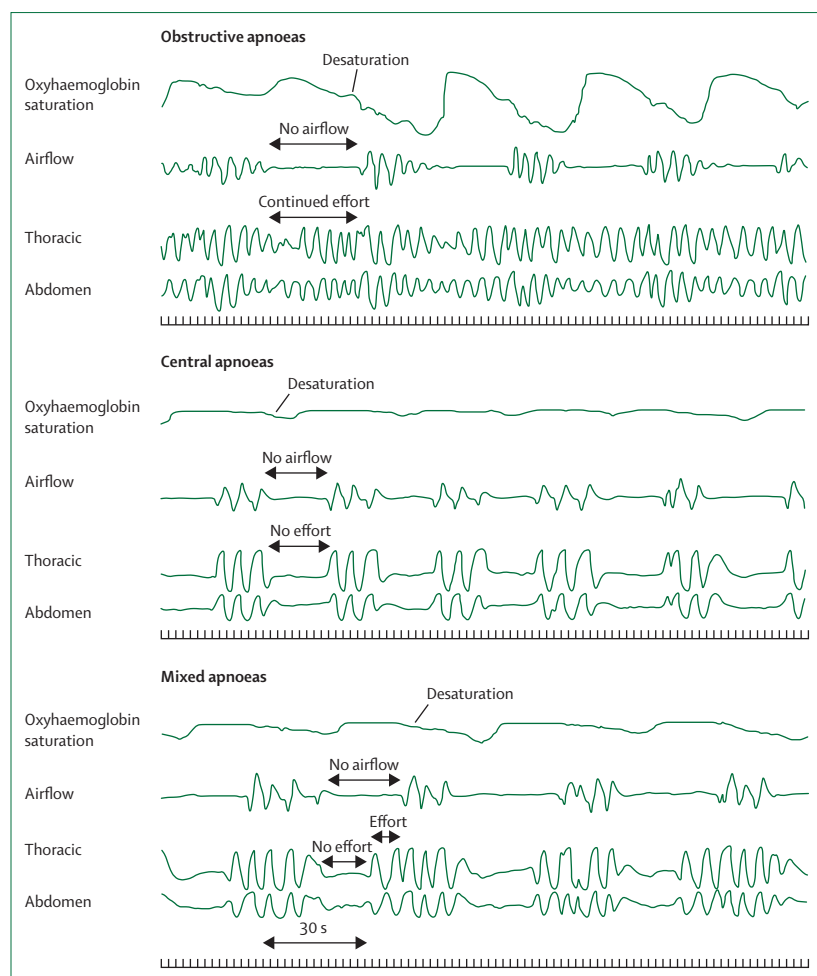
Figure 1: 3-min recordings characteristic of obstructive, central, and mixed apnoeas during sleep
Traces shown represent oxyhaemoglobin saturation, airflow, and thoracic and abdominal movement.

oral glucose tolerance test. In addition to these four categories of diabetes, two prediabetic disorders of clinical relevance include impaired fasting glucose and impaired glucose tolerance. Impaired fasting glucose is defined as a fasting glucose concentration between 100 mg/dL and 126 mg/dL. Impaired glucose tolerance is defined as a 2-h post-challenge glucose concentration between 140 mg/dL and 200 mg/dL during the oral glucose tolerance test.[7]

Obstructive sleep apnoea and glucose metabolism

Evidence for an association

In the past two decades, research focusing on the effects of obstructive sleep apnoea on glucose metabolism has increased substantially. Initial studies were important in detecting an association between obstructive sleep apnoea and metabolic dysfunction. However, many of the early studies were burdened with methodological limitations, such as small sample sizes, use of self-reported symptoms to define obstructive sleep apnoea

(eg, snoring and witnessed apnoeas), and inadequate consideration of confounders such as obesity, thereby making interpretation of results challenging.[8] Although most of the initial studies were cross-sectional, two epidemiological studies[9,10] were pivotal in showing a causal association by demonstrating a higher incidence of diabetes in people with obstructive sleep apnoea-associated symptoms than in those without symptoms.[9,10] Subsequent observational studies[11,12] filled in many of the major gaps noted in earlier reports through the use of polysomnography to characterise obstructive sleep apnoea and by considering the effects of obesity by statistically accounting for body-mass index, waist circumference, or both. Most observational studies have shown that measures of obstructive sleep apnoea severity, such as the AHI and degree of oxyhaemoglobin desaturation during sleep, were associated with metabolic abnormalities.[12–14] In particular, data from the Sleep Heart Health Study[15] were key in the establishment of independent cross-sectional associations between obstructive sleep apnoea severity, insulin resistance, and fasting and post-glucose challenge hyperglycaemia in a large community cohort of middle-aged and elderly adults (age ≥40 years). Specifically, an AHI of 15 or more events per h was associated with lower insulin sensitivity and a higher prevalence of impaired fasting glucose and glucose intolerance. Longitudinal data with polysomnographically defined obstructive sleep apnoea are scarce but seem to substantiate the possibility of a causal role for obstructive sleep apnoea in metabolic dysfunction.[16,17] Collectively, the available evidence confirms that association between obstructive sleep apnoea and metabolic dysfunction does exist and is independent of confounders such as obesity. However, additional prospective data from adequately powered cohort studies are needed to further corroborate the hypothesis for a causal effect. If such longitudinal data eventually show that obstructive sleep apnoea is a precursor of abnormalities in glucose metabolism, what are the causal pathways that underlie the association?

Causal links

Little controversy exists that intermittent hypoxia and recurrent arousals from sleep, the two pathophysiological concomitants of obstructive sleep apnoea, are likely to mediate the metabolic dysfunction observed in obstructive sleep apnoea. Several studies in animal models have shown that exposure to hypoxia (sustained or intermittent) can perturb normal glucose homoeostasis[18]—eg, by increasing fasting insulin concentrations.[19–22] Similarly, healthy participants show impairments in insulin sensitivity when exposed to sustained or intermittent hypoxia,[23–26] which corroborates the hypothesis that hypoxia can adversely affect glucose metabolism. Furthermore, disruption of normal sleep continuity from recurrent arousals in obstructive sleep apnoea can also negatively affect glucose metabolism. Apart from sleep fragmentation, sleep duration, especially habitual sleep
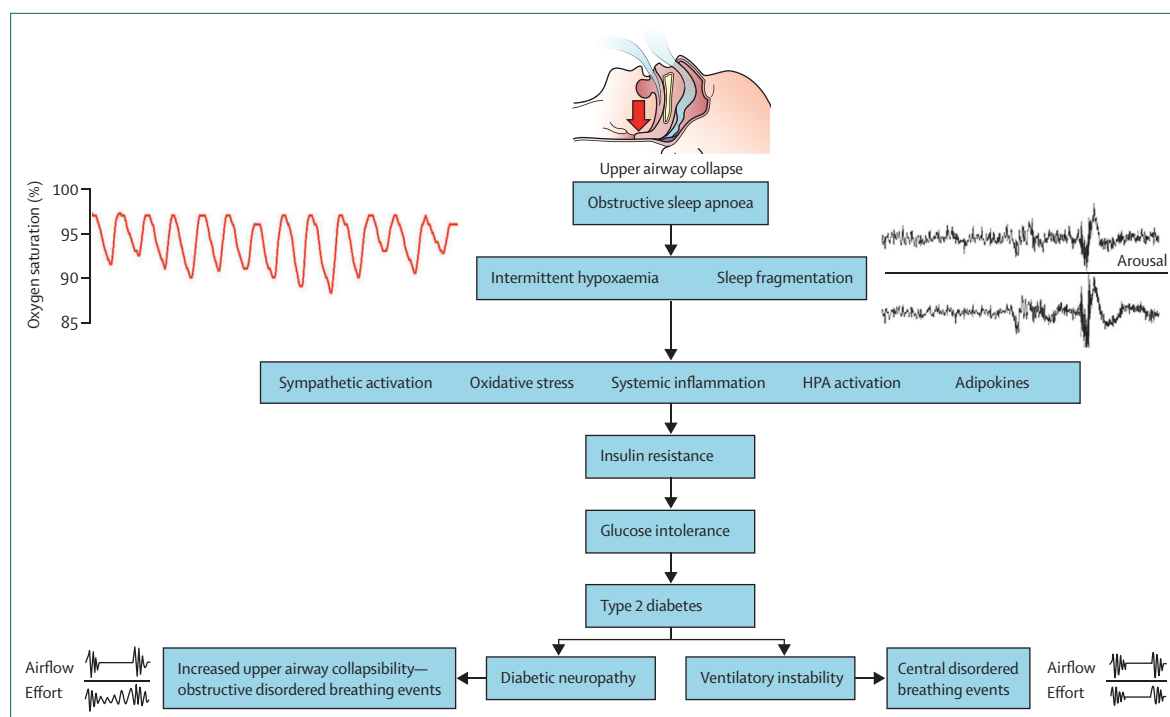
Figure 2: **Causal pathways linking obstructive sleep apnoea, insulin resistance, glucose intolerance, and type 2 diabetes**
HPA=hypothalamic–pituitary–adrenal.

duration of less than 6 h per night, has also been shown to negatively affect glucose metabolism.[27–30] Although recurrent arousals from sleep might curtail total sleep time, sleep duration and sleep fragmentation should be recognised as pathophysiologically distinct, and the former can be preserved, even with repetitive arousals from sleep. Despite the fact that empirical data for the effects of sleep fragmentation are scarce, two independent groups have shown negative effects of sleep fragmentation on insulin sensitivity in healthy participants.[31,32] However, the intermediate pathways through which intermittent hypoxaemia and sleep fragmentation affect glucose metabolism are not well understood. Figure 2 shows potential mechanisms that might explain the association between obstructive sleep apnoea and metabolic dysfunction; these mechanisms include activation of the sympathetic nervous system; changes in activity of the hypothalamic–pituitary–adrenal (HPA) axis; formation of reactive oxygen species; and increases in inflammatory cytokines (ie, interleukin 6 and tumour necrosis factor α) and adipocyte-derived factors (ie, leptin, adiponectin, and resistin).

Patients with obstructive sleep apnoea show higher sympathetic neural activity during sleep and wakefulness, as shown by sympathetic nerve activity recordings, and higher plasma and urinary catecholamines which decrease with treatment of obstructive sleep apnoea.[33] Acute hypoxaemia can activate the sympathetic nervous system and hypercapnia can further enhance this

response.[34,35] Moreover, observational and experimental evidence has shown that even brief arousals from sleep can lead to surges in sympathetic activity.[36] Thus, the combined effects of intermittent hypoxaemia and recurrent arousals in obstructive sleep apnoea can shift autonomic balance towards increased sympathetic activity. The sympathetic nervous system has a central role in regulation of glucose and fat metabolism.[13] Although the exact mechanisms are not well characterised, catecholamines reduce insulin-mediated glucose uptake, decrease insulin sensitivity, promote pancreatic β cell apoptosis, and impair insulin secretion.[37,38] Furthermore, catecholamines can inhibit insulin-mediated glycogenesis, increase glycolysis, and reduce the ability of glucose to stimulate its own disposal.[37,39] Raised sympathetic activity also has lipolytic effects, resulting in increases in circulating free fatty acids, which, in turn, can worsen by decreasing insulin sensitivity. Finally, sympathetic nervous system-mediated vasoconstriction can shunt glucose and insulin from skeletal muscle to less metabolically active areas with consequent decreases in net glucose uptake.[18,40] Thus, substantial data exist to implicate sympathetic nervous system activation in obstructive sleep apnoea as a central mechanism of metabolic dysfunction.

Oxidative stress is characterised by a state in which the production of reactive oxygen species exceeds antioxidant defences. In obstructive sleep apnoea, repetitive cycles of hypoxaemia followed by reoxygenation increase the

production of reactive oxygen species, a pattern that is also seen in ischaemia–reperfusion injury. In fact, recent data suggest that obstructive sleep apnoea is associated with high concentrations of reactive oxygen species.[41] Differences in lipid peroxidation, isoprostane concentrations, and markers of DNA oxidation have been recorded between patients with obstructive sleep apnoea and healthy people. Studies assessing the effects of obstructive sleep apnoea treatment have also shown a decrease in several reactive oxygen species with positive airway pressure treatment.[40] Excessive concentrations of reactive oxygen species can inhibit insulin-stimulated substrate uptake in muscle and adipose tissue and potentially damage pancreatic β cells because of the relatively low concentrations of antioxidant enzymes in these cells. Thus, oxidative stress is a potentially important intermediate that could contribute to altered glucose metabolism in obstructive sleep apnoea.[40,42]

Adipokines are biologically active factors that are secreted by adipocytes and affect energy and glucose homoeostasis. Specifically, adipocyte-derived factors such as leptin, adiponectin, and resistin are thought to be integral in the genesis of obesity-related abnormalities in glucose metabolism.[43] Centrally, leptin regulates hunger and weight gain by increasing anorexigenic and decreasing orexigenic neuropeptide expression in the hypothalamus.[44] Peripherally, leptin seems to be involved in glucose homoeostasis.[45] A state of leptin resistance persists in obesity that is unresponsive to exogenous leptin administration. Patients with obstructive sleep apnoea have raised leptin concentrations, even after obsesity has been accounted for, and treatment with positive airway pressure seems to reduce these concentrations.[46] However, whether raised leptin concentrations have a role in mediating insulin resistance and metabolic dysfunction in obstructive sleep apnoea remains to be established.[13]

Adiponectin is also synthesised by the adipocyte and is thought to have insulin-sensitising properties.[47] Low circulating adiponectin is a risk factor for incident diabetes, atherosclerosis, and dyslipidaemia.[47,48] Studies in animals have shown that the absence of adiponectin is associated with insulin resistance, and high adiponectin concentrations in human studies have been protective against diabetes.[49–51] Additionally, adiponectin concentrations have been found to be lower in patients with obstructive sleep apnoea than in healthy people. Furthermore, adiponectin concentrations seem to correlate inversely with oxygen saturation. Thus, with increased severity of oxygen desaturation, serum adiponectin concentrations increase. However, as is the case for leptin, adiponectin's role in obstructive sleep apnoea-related abnormalities in glucose metabolism is not well defined.[18,40] Resistin is the third adipokine of interest in obstructive sleep apnoea. Initially, resistin was thought to increase hepatic insulin resistance and impair glucose tolerance.[52,53] However, more recent studies have challenged this notion, making the relevance of resistin to diabetes unclear.[54] Data for whether resistin concentrations differ between people with and without obstructive sleep apnoea are scarce. Thus, although our increasing knowledge of adipocyte biology indicates that substances produced by fat are crucial in mediating insulin resistance, additional work is needed to establish how individual adipokines are affected by intermittent hypoxaemia and recurrent arousals, and whether these factors have any role in the mediation of metabolic dysfunction in obstructive sleep apnoea.

Obstructive sleep apnoea could also affect glucose homoeostasis by modulating the HPA axis. Both intermittent hypoxaemia and sleep fragmentation could lead to excessive cortisol secretion by provoking a stress-related increase in HPA activity. Data from studies of high altitude and hypobaric conditions indicate that hypoxia modifies the diurnal pattern of the HPA axis and increases circulating cortisol concentrations.[42] Moreover, brief arousals or sustained awakenings from sleep can activate the HPA axis and can further increase corticotropic function. Cortisol and other glucocorticoids interfere with glucose metabolism by increasing hepatic glucose production, decreasing insulin-dependent glucose uptake into peripheral tissues, and inhibiting insulin release from pancreatic β cells.[13,18,40] Although a wealth of indirect evidence exists to provide a biological basis for the negative effect of obstructive sleep apnoea on the HPA axis and consequently on glucose metabolism, the exact role of HPA activity in metabolic dysfunction in obstructive sleep apnoea needs further research.

The presence of a chronic inflammatory state marked by a low grade but persistent increase in inflammatory markers in obstructive sleep apnoea has triggered interest in whether inflammatory pathways could potentially explain its effect on vascular disease. Substantial evidence indicates that patients with obstructive sleep apnoea have raised circulating concentrations of inflammatory markers such as C-reactive protein, interleukin 6, circulating adhesion molecules, and tumour necrosis factor α.[55] A valid concern is that most inflammatory markers are nonspecific and can be raised because of the effects of other factors such as age and visceral adiposity. Parallel lines of evidence have converged to implicate subclinical inflammation in the pathogenesis of insulin resistance and diabetes.[42] The prospective design of many of the available studies provides compelling evidence for a causal, rather than a correlative, association with low-grade systemic inflammation that persists for years before the onset of type 2 diabetes. Thus, the inflammatory effects of obstructive sleep apnoea might predispose to altered glucose metabolism. Additional research is clearly needed to help further define the significance of this potential link between obstructive sleep apnoea and subclinical inflammation in the context of abnormal glucose homoeostasis.[13,18,40]

Despite the amalgamation of both epidemiological and experimental evidence showing an independent association between obstructive sleep apnoea and metabolic dysfunction, interventional studies of positive airway pressure treatment and glucose metabolism have not generally been consistent in showing a favourable effect. In view of the fact that positive airway pressure treatment mitigates intermittent hypoxia and sleep fragmentation, it can be reasonably assumed to have a positive effect on glucose homoeostasis. However, results from studies of the effects of this treatment on various parameters of glucose metabolism have been conflicting.[11,12,56–59] The absence of a consistent effect might be related to the small study samples, suboptimum adherence to positive airway pressure treatment, and the variability in measures used to characterise glucose homoeostasis and glycaemic control. Recently, Sharma and colleagues[60] showed a decrease in the prevalence of metabolic syndrome in a community-based trial of positive airway pressure treatment for obstructive sleep apnoea. Improvements in total cholesterol, triglyceride concentrations, and blood pressure were recorded with positive airway pressure treatment. However, no differences were noted in glycated haemoglobin or insulin sensitivity, and the improvement in metabolic syndrome was mainly due to a decrease in blood pressure and favourable changes in lipid profiles. Although this study emphasises the potential benefits of positive airway pressure treatment in patients with metabolic syndrome and provides some insight, several limitations make interpretation of the results difficult. For example, can the improvement in metabolic syndrome be attributed to the weight loss seen with positive airway pressure treatment? Clearly, well-designed, randomised controlled trials are needed to clarify whether positive airway pressure treatment improves glucose metabolism in the absence of any changes in weight or other confounding variables, such as activity levels.

Effect of glycaemia on sleep-disordered breathing
Glycaemia and obstructive sleep apnoea
Although the discussion so far has focused on the possibility of obstructive sleep apnoea contributing to metabolic dysfunction, the possibility of reverse causality also exists. Once diabetes develops, can it then contribute to the incidence of obstructive sleep apnoea, or the worsening of symptoms that are already present? Indeed, many studies have shown a higher prevalence (range 54–94%) of obstructive sleep apnoea in patients with diabetes than in their nondiabetic counterparts.[61–63] However, a high prevalence of obstructive sleep apnoea in patients with diabetes is in itself insufficient to prove a causal link between diabetes and obstructive sleep apnoea, especially in view of the confounding effect of obesity.[62,64] Investigations of the occurrence and temporal progression of obstructive sleep apnoea in patients with diabetes are scarce but the possibility that diabetes could worsen obstructive sleep apnoea severity has been noted.[65–69] Experimental data from animal models show that insulin resistance is associated with a reduced ventilatory response that can be prevented by insulin treatment.[70] Whether such abnormalities in ventilatory control have long-term biological or clinical consequences, such as exacerbating or causing sleep-disordered breathing, possibly by promoting apnoeas and hypopnoeas during sleep, is not known. Longitudinal studies will hopefully clarify whether progression of obstructive sleep apnoea differs between diabetic and non-diabetic patients.

Glycaemia and central sleep apnoea
In addition to the possibility that metabolic dysfunction and diabetes might change the progression of obstructive sleep apnoea, evidence also suggests that diabetes could promote the occurence of central sleep apnoea. Resnick and colleagues[64] showed that patients with type 2 diabetes from the community-based Sleep Heart Health Study had a higher prevalence of periodic breathing and central respiratory events during sleep than those without diabetes. The higher prevalence of periodic breathing in patients with diabetes than in non-diabetics (odds ratio 1·74) persisted even after accounting for several covariates including age, sex, body-mass index, and prevalent cardiovascular disease. Diabetes-associated autonomic dysfunction might affect respiratory control through enhanced central chemoreceptor-mediated gain and thus predispose to periodic breathing during sleep. There is some evidence that patients with diabetes and autonomic neuropathy might have a heightened response to hypercapnia.[71] This evidence, combined with the many clinical case series,[72–74] suggests that central sleep-disordered breathing is prevalent in diabetes, particularly with concurrent autonomic dysfunction.

During sleep, patency of the upper airway depends on both mechanical and functional properties. Mechanical effects include factors that anatomically affect upper airway diameter (eg, parapharyngeal fat deposition in obstructive sleep apnoea), whereas functional aspects would encompass upper airway reflex responses, peripheral control of the upper airway muscles, mechanoreceptor activation thresholds, central ventilatory control and stability, and peripheral responses to hypercapnia and hypoxia. Autonomic neuropathy associated with diabetes could disrupt these functional processes and promote the development of obstructive events during sleep by reducing upper airway calibre. Indeed, patients with diabetes-associated autonomic neuropathy have a higher prevalence of obstructive sleep apnoea than do those with diabetes without autonomic dysfunction.[66,75,76] Additionally, compared with patients with diabetes without autonomic neuropathy and nondiabetic controls, diabetics with autonomic neuropathy have been shown to have more severe obstructive sleep apnoea, a longer duration of respiratory events, and more severe oxygen desaturations.[66–69]

Establishment of whether a causal effect exists whereby metabolic dysfunction and diabetes increase the risk of obstructive and central sleep apnoea is of clinical value. Although the prevalence of obstructive sleep apnoea is high in diabetic patients, it remains severely underdiagnosed. Inadequate case identification is partly due to an absence of awareness by health-care providers of the epidemiology and clinical consequences associated with obstructive and central sleep apnoea. Another factor adding to this absence of awareness is that diabetic patients do not necessarily present with symptoms that are typical of obstructive sleep apnoea.[67,77] Thus, recognition of the co-existence of metabolic and sleep-related breathing disorders is crucial to address the unmet needs of affected patients and curtail the multiplicative cardiovascular risk from the two disorders. Tamura and colleagues[78] showed that obstructive sleep apnoea and sleep-related hypoxia are associated with higher glycated haemoglobin concentrations, irrespective of glycaemic status (normal glucose tolerance, impaired glucose tolerance, or overt diabetes mellitus). These findings confirm previous reports showing similar impairments in glycaemic status in obstructive sleep apnoea patients with or without diabetes.[10,79] The clinical implications of glycaemic status and poor glycaemic control (ie, glycated haemoglobin) for cardiovascular risk are incontrovertible. Thus, the presence of untreated obstructive sleep apnoea in diabetes could signify a worse prognosis and warrant more aggressive screening and management of obstructive sleep apnoea in patients with diabetes. Treatment of obstructive sleep apnoea might improve medical management of diabetes in the form of de-escalation of oral hypoglycaemic medications in a manner similar to that reported with antihypertensive drug treatment in patients with resistant hypertension.[80] Finally, chronic hyperglycaemia is well known to induce oxidative stress, with resultant structural nerve damage and nerve dysfunction.[81] The additional oxidative stress caused by untreated obstructive sleep apnoea-associated hypoxia could exacerbate nerve damage and worsen autonomic dysfunction, further aggravating sleep-disordered breathing and creating a recurring vicious cycle.

Therapeutic considerations common to obstructive sleep apnoea and diabetes

The primary focus of treatment for obstructive sleep apnoea is to prevent upper airway collapse during sleep with mechanical methods such as positive airway pressure treatment, mandibular advancement devices, or upper airway surgery.[82] Although all these treatment approaches increase airway patency during sleep with variable efficacy, none address the underlying problem of obesity, which is by far the strongest risk factor for obstructive sleep apnoea. Epidemiological data from the Wisconsin Sleep Cohort Study[83] and the Sleep Heart Health Study[84] have shown that weight loss can lead to substantial improvements in obstructive sleep apnoea severity through changes in structure and function of the upper airway. Irrespective of whether the weight loss is achieved through dietary, medical, or surgical methods, improvements have been documented not only in obstructive sleep apnoea severity but also in accompanying sleep quality and daytime sleepiness.[85] Exercise and increased physical activity have a beneficial effect on obstructive sleep apnoea severity and daytime performance, which is not explained entirely by accompanying weight loss.[86] In view of the fact that decreasing bodyweight can have favourable effects on glycaemic control, the goal of weight reduction or at least weight maintenance is a cornerstone in the management of diabetes-related hyperglycaemia.[87] Moreover, moderate physical activity can substantially reduce the risk of diabetes development in patients with impaired glucose tolerance and can help with glycaemic control in patients with established diabetes.[88] Thus, the institution of lifestyle interventions as an adjunct to positive airway pressure treatment will not only accomplish the therapeutic goals for obstructive sleep apnoea but also has the potential to be curative in the long term. Similarly, in patients with diabetes, initiation of positive airway pressure treatment for untreated obstructive sleep apnoea could improve glycaemic control by mitigating the adverse effects of intermittent hypoxaemia and sleep disruption. More importantly, the treatment of obstructive sleep apnoea in diabetes will certainly ameliorate daytime sleepiness and fatigue, thus empowering those affected to engage in lifestyle modifications that will positively affect glycaemic control and consequent cardiovascular risk.

Future directions

Despite enormous progress in the past two decades, many challenges remain in unravelling the bidirectional link between obstructive sleep apnoea and diabetes (table). First, establishment of which glycaemic measures are most indicative of obstructive sleep apnoea-related changes in glucose homoeostasis has been problematic. Outcome measures reported in published studies have varied greatly and include static measures such as fasting glucose and insulin or glycated haemoglobin concentrations as markers of insulin resistance and glycaemic control, respectively. The use of such crude or static measures of glycaemic status does not fully characterise the problems in glucose disposal and could explain the discrepancies between studies of positive airway pressure treatment. Furthermore, improvements in glycaemic measures with positive airway pressure treatment in the setting of already well controlled diabetes might not be achievable (ie, a so-called floor effect) and might also explain the discrepancies in studies of the effects of positive airway pressure treatment on glucose and insulin homoeostasis. Perhaps positive airway pressure treatment for obstructive sleep apnoea is likely to have a

favourable effect on glycaemic control if underlying diabetes is not controlled well. Likewise, if a specific risk factor (ie, obstructive sleep apnoea) is more severe, its overall contribution to metabolic derangements is likely to be more substantial. Therefore, a favourable effect on metabolic outcomes is plausible with treatment of severe obstructive sleep apnoea rather than mild or moderate disease,[89] in which hypoxic stress is not likely to be so detrimental. Thus, future studies of metabolic dysfunction in obstructive sleep apnoea need to more consistently stratify the severity of obstructive sleep apnoea to fully characterise the effects of positive airway pressure treatment on glycaemic measures.

Additionally, disease duration for both obstructive sleep apnoea and metabolic abnormalities adds another degree of complexity that is important but has not been addressed consistently in the scientific literature. Development of hyperglycaemia and diabetes is well recognised to be a multistep process along a continuum that is affected substantially by genetic and environmental factors. The natural history of diabetes is characterised at the outset by normal glucose tolerance, followed initially by insulin resistance and compensatory hyperinsulinaemia. Eventually, glucose intolerance develops, with failure of pancreatic β cells, and finally culminates in the clinical expression of diabetes and its associated complications. The presence of untreated obstructive sleep apnoea with its concomitants of intermittent hypoxia and sleep fragmentation could even accelerate progression of diabetes along this pathway. Similarly, the duration of obstructive sleep apnoea might also affect glucose regulation. Disease chronicity is a well-established key

factor that can affect response to treatment and should be more clearly addressed in future research efforts.

Duration and adherence to positive airway pressure treatment is another crucial issue that has made interpretation of interventional studies difficult. Variability in duration and poor adherence to positive airway pressure treatment can affect reported outcome measures of glucose homoeostasis. Published studies of positive airway pressure therapy use in hypertensive patients have suggested that only after sustained use are falls in mean arterial pressures evident.[80] The same result could also be true for glucose metabolism. Thus, clinical trials with sustained positive airway pressure treatment use would be more meaningful to establish whether treatment for obstructive sleep apnoea actually improves glucose metabolism.

In addition to the issue of adherence to positive airway pressure treatment, confounding by obesity is still one of the most pivotal issues in the area of research relating obstructive sleep apnoea and glucose metabolism. Accounting for body-mass index is no longer sufficient to account for elements, such as fat distribution or body fat percentage, that probably affect the association between obstructive sleep apnoea and glucose metabolism or the effects of continuous positive airway pressure treatment on glycaemic measures. Quantitative methods that provide an assessment of percentage body fat (eg, DEXA scan) and visceral fat mass (MRI or CT scan) need to be part of future investigations, including randomised clinical trials.

Although the issues outlined in the table represent formidable challenges for future research efforts, only by consideration of these issues can relevant questions

	Proposed solution
Characterise the association between sleep apnoea and glucose metabolism, while accounting for visceral adiposity	Assess visceral fat with CT or MRI and measure of glucose metabolism in a group of patients with varying degrees of obstructive sleep apnoea severity to assess independent associations
Define whether factors such as age, sex, and race affect the metabolic consequences of sleep apnoea	Epidemiological or clinical study to survey effect modification of the association between obstructive sleep apnoea and metabolic dysfunction by age, sex, and race
Advance basic and clinical research into delineating mechanisms that explicate the metabolic effects of sleep apnoea	Animal and human studies that assess the independent effects of intermittent hypoxaemia and arousals on various physiological axes that regulate glucose and insulin homeostasis
Assess the effects of sleep apnoea treatment with positive airway pressure on metabolic outcomes	Clinical trials assessing effect of sleep apnoea treatment on glycaemic measures in prediabetes and diabetes (NCT01156116, NCT01136785, and NCT00509223)
Define the change in sleep apnoea severity in those with and without type 2 diabetes	Longitudinal assessment of the change in sleep apnoea severity in people with and without diabetes (NCT00031239)
Assess the usefulness of combination treatments in obstructive sleep apnoea on glycaemic control	Clinical trials that include multimodal interventions (positive airway pressure treatment, weight loss, and exercise) compared with positive airway pressure therapy alone
Delineate whether and how type 2 diabetes can increase predisposition for obstructive and central sleep apnoea	Physiological studies that characterise upper airway collapsibility and ventilatory control parameters in people with and without type 2 diabetes mellitus
Establish whether treatment of central and obstructive sleep apnoea in patients with type 2 diabetes curtails cardiovascular risk	Randomised clinical trials that assess the effects of positive airway pressure therapy in people with type 2 diabetes and sleep apnoea to measure improvements in markers of cardiovascular risk, such as blood pressure, serum lipids, endothelial function, and circulating inflammatory markers
How do milder forms of disordered breathing during sleep (eg, snoring and flow limitation) and mild sleep apnoea change glucose and insulin homoeostasis?	Undertake epidemiological studies that define the effect of early stages of sleep apnoea on glucose metabolism and, conversely, how milder metabolic impairments affect breathing abnormalities during sleep

Table: **Research agenda for obstructive sleep apnoea and type 2 diabetes**

Search strategy and selection criteria

To provide a critical appraisal of the published literature and to emphasise the most recent research on the link between obstructive sleep apnoea and diabetes, an online search was done using the PubMed database. A Boolean strategy was used, which encompassed the search terms "sleep apnea" and ("insulin resistance" or "glucose intolerance" or "diabetes") to search for articles published from January, 1966, to January, 2013 . The only restrictions applied were that the articles were published in English and were not case studies or published only in abstract form. Abstracts from the resulting search were reviewed and articles most pertinent to the subject are included.

about the bidirectional association between obstructive sleep apnoea and diabetes be addressed. Little is known about how the early stages of obstructive sleep apnoea affect glycaemia and how mild metabolic impairment affects breathing abnormalities during sleep. A better understanding of whether obstructive sleep contributes to metabolic abnormalities and whether metabolic dysfunction, once established, accelerates the natural history of obstructive and central sleep apnoea is paramount for the clinical care of all of those affected with one or both of these disorders. Irrespective of the directionality of causal effects, health-care professionals who care for patients with obstructive sleep apnoea or diabetes should incorporate screening methods to ensure that a patient presenting with one disorder is assessed for the other. Under-recognition of sleep apnoea undoubtedly impedes our ability to understand the association between these two prevalent disorders. Equally importantly, failure to diagnose obstructive sleep apnoea can adversely affect several major clinical outcomes. Early recognition and treatment of obstructive sleep apnoea is especially crucial in light of burgeoning evidence implicating the disorder as an independent risk factor for cardiovascular disease.[90] In those already at risk for cardiovascular disease because of diabetes, treatment of obstructive sleep apnoea with positive airway pressure could be especially valuable. However, rigorous and adequately powered trials are now desperately needed to justify the early identification and treatment of obstructive sleep apnoea in people with diabetes. In future studies, and in clinical practice, treatment of obstructive sleep apnoea should be multimodal and should include diet, exercise, and weight loss, in addition to positive airway pressure therapy. Multimodal treatment not only has the potential to improve obstructive sleep apnoea severity[91–94] but may also independently confer cardiovascular and metabolic benefits.[95] Future studies ascertaining synergistic effects between continuous positive airway pressure therapy and weight loss or exercise on glucose homoeostasis would also be enormously worthwhile. Finally, in view of the fact that not every person with obstructive sleep

apnoea can tolerate positive airway pressure treatment, the effects of alternative treatment strategies on glucose homeostasis, such as healthy lifestyle changes, upper airway surgery, and oral devices, should also be investigated. Early case identification and treatment of each disorder can decrease cardiovascular risk and improve quality of life.

Conclusions

Obstructive sleep apnoea is common in individuals with diabetes, with an estimated prevalence of 60–80%.[62] Moreover, almost two-thirds of those affected by diabetes have moderate to severe obstructive sleep apnoea that would warrant positive airway pressure treatment. Despite the well-established coexistence and bidirectional nature of the association between obstructive sleep apnoea and diabetes, additional data are needed to define the likelihood of diabetes development in patients with obstructive sleep apnoea and its natural history. Although future studies will better define the time course of metabolic dysfunction in obstructive sleep apnoea and conversely the development and progression of this disorder in individuals with diabetes, irrefutable evidence now supports the need to screen patients affected by one disorder for the other. Inquiry about sleep-related symptoms in patients with diabetes or screening of patients with obstructive sleep apnoea for hyperglycaemia can be done easily, and these approaches hold immense potential for curtailment of the adverse cardiovascular and non-cardiovascular outcomes associated with each disorder.

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