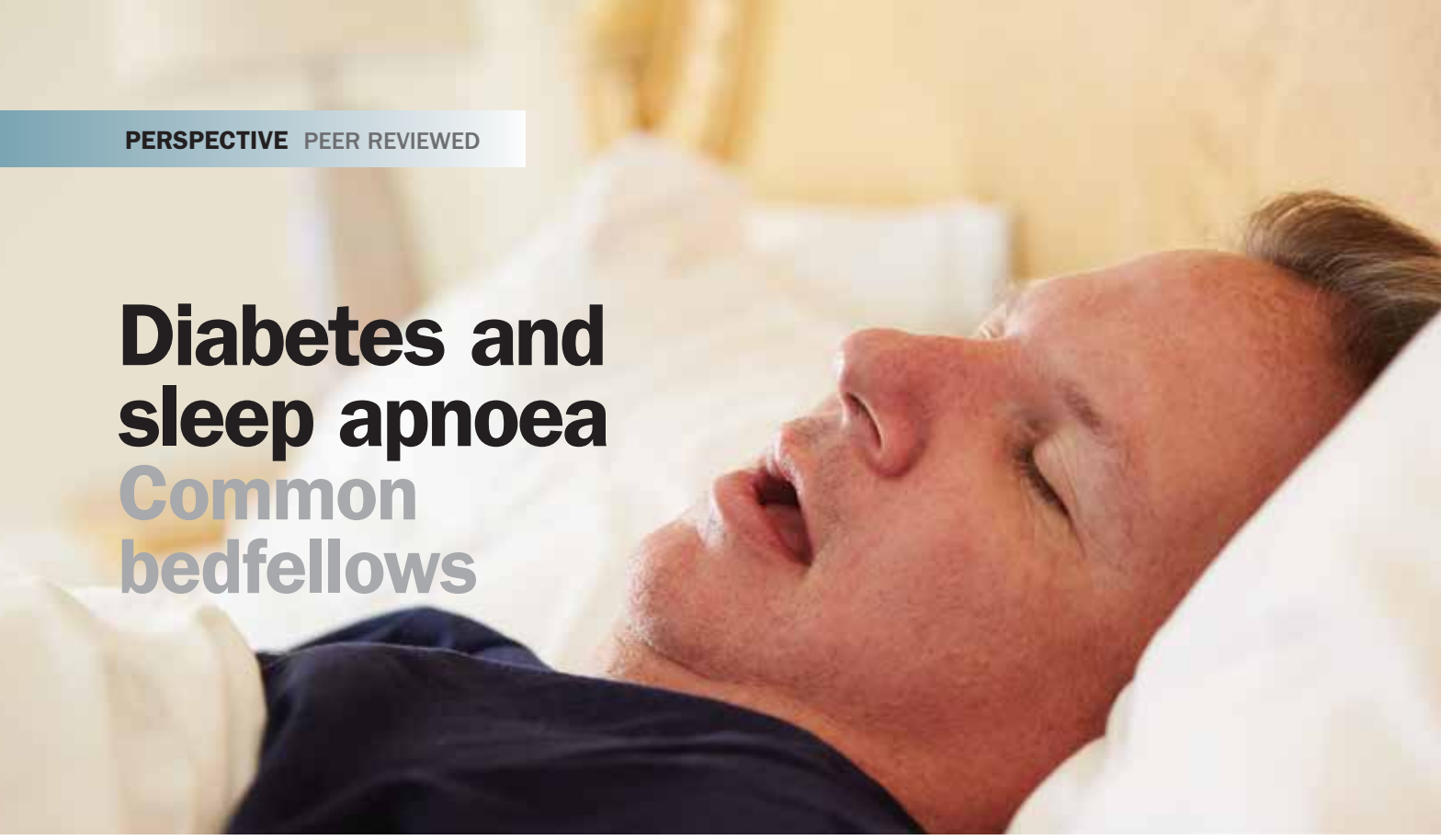

Diabetes and sleep apnoea
Common bedfellows

LILI HUO MD
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Key points

- **Sleep apnoea is a significant health problem in the general community, especially in people with diabetes.**
- **Sleep apnoea is associated with insulin resistance, glucose intolerance and diabetes, independently of obesity.**
- **The prevalence of sleep apnoea in patients with diabetes and obesity has been reported to be as high as 86%.**
- **Intermittent hypoxaemia and fragmented sleep in patients with sleep apnoea trigger a wide range of pathophysiological mechanisms that may aggravate insulin resistance and glucose metabolism. Diabetes may contribute to sleep apnoea via neuropathy and weight gain related to medication use.**
- **Treatment of sleep apnoea is associated with improvements in daytime sleepiness and quality of life, and may also have a favourable impact on glycaemic control.**
- **Given the high prevalence of sleep apnoea and diabetes, and their strong associations with each other, the presence of one condition should actively prompt screening for the other, especially in the setting of obesity.**

Diabetes and sleep apnoea share several risk factors, including advancing age, obesity, hypertension and impaired glucose tolerance. The two conditions commonly coexist and may interact synergistically to increase the risk of cardiovascular disease. Heightened awareness of the need to consider screening for sleep apnoea in people with diabetes and also for diabetes in people with sleep apnoea is necessary.

Sleep apnoea is increasingly recognised as a significant health problem in the general community, particularly in people with diabetes. An ever growing number of studies have shown that sleep apnoea is associated with insulin resistance, glucose intolerance and diabetes, independently of obesity. Diabetes and sleep apnoea share several risk factors, including advancing age, obesity, hypertension and impaired glucose tolerance. Both conditions commonly coexist and may interact synergistically to increase the risk of cardiovascular disease.

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This article discusses the bidirectional association between sleep apnoea and diabetes, and the implications that this has for both screening and management of the two conditions.

Sleep apnoea

Sleep apnoea is characterised by the occurrence of disordered breathing events during sleep. These events include pauses in breathing and shallow breaths during sleep. Each pause in breathing (an apnoea) can last for at least 10 seconds in duration, and may occur five to 30 times or even more in an hour. Similarly, each abnormally shallow breathing event (a hypopnoea) involves a decrease in airflow for at least 10 seconds associated with an arousal on electroencephalogram and/or desaturation. The apnoea–hypopnoea index (AHI), which is the number of apnoeas and hypopnoeas per hour of sleep, is the most commonly used disease-defining metric for sleep apnoea. This leads to the following classification: normal (AHI <5 events per hour), mild (AHI 5.0–14.9 events per hour), moderate (AHI 15.0–29.9 events per hour) or severe (AHI ≥30 events per hour). Symptoms of sleep apnoea are listed in the Box.[1]

There are three forms of sleep apnoea and these are obstructive, central and mixed sleep apnoea, constituting 84%, 0.4% and 15% of cases, respectively.[2] Mixed sleep apnoea involves a combination of central and obstructive sleep apnoea in the same person. The classification of an event as obstructive or central depends on whether, in the absence of airflow, there is ongoing respiratory effort.

Obstructive sleep apnoea (OSA) is the most prevalent type of sleep apnoea. OSA is characterised by recurrent episodes of upper airway obstruction during sleep coinciding with increased inspiratory efforts and resulting in hypoxia and arousal from sleep leading to fragmented sleep and excessive daytime sleepiness. Up to 24% of men and 9% of women may have clinically significant OSA, which approximates to nearly two million Australians. OSA is a treatable sleep disorder that is more prevalent in overweight and obese adults. Untreated OSA can cause high blood pressure and other cardiovascular diseases,[3,4] and is also a major contributor to workplace accidents and driving-related accidents.[5,6]

Sleep apnoea and diabetes: what's the link?

A number of cross-sectional studies have demonstrated that OSA is independently associated with insulin resistance and diabetes. The prevalence of OSA in patients with diabetes has been reported to vary between 23% and 86%, with differences in study populations and definitions of OSA explaining the large variation.[7-9] The highest estimate of 86% was reported in obese patients with diabetes enrolled in the multicentre Sleep Action for Health in Diabetes (AHEAD) study.[8]

Accumulating evidence also suggests that there is a significant association between OSA and retinopathy and maculopathy, independent of conventional risk factors for retinopathy, in patients with diabetes.[10,11] These findings suggest that OSA is largely unrecognised in patients with diabetes.

Symptoms of sleep apnoea[1]

Cardinal features of sleep apnoea

- A history of habitual snoring
- A record of witnessed apnoeas
- Excessive daytime sleepiness

Associated symptoms of sleep apnoea

- Fatigue, sleepiness during the day, loss of energy
- Irritability
- Poor memory
- Depression
- Mood changes
- Morning headaches
- Sexual dysfunction
- Nocturia

Similarly, the prevalence of diabetes in patients with OSA is high, and ranges from 15 to 30%, depending on the study population and the measurement parameters used to diagnose OSA and diabetes.[12-16] Furthermore, there is evidence that the worse the sleep apnoea, the greater the risk of glucose intolerance.[13,15,17-20] In an 11-year follow-up study, the deterioration of insulin sensitivity was associated with the severity of sleep breathing disorder at baseline.[20]

However, in some studies the association between sleep apnoea and glucose intolerance was no longer observed after adjusting for confounders.[15] Thus, there remains a degree of uncertainty over the independence of this relationship.

Pathophysiological links between diabetes and OSA

With growing recognition of the comorbidity between OSA and diabetes, it is important to understand the potential pathophysiological links between the two diseases. Most work has focused on the role of intermittent hypoxaemia and sleep fragmentation in influencing glucose metabolism. These two central characteristics of sleep apnoea have been shown to alter sympathetic nervous system activity and activity of hypothalamic–pituitary axis, cause oxidative stress, and influence inflammatory pathways and adipokine profiles (see Figure).[21-24]

Autonomic neuropathy, a complication of diabetes, may increase the risk of developing OSA, thus creating a vicious cycle between diabetes and OSA. Weight gain related to insulin and sulfonylurea use may also predispose patients with diabetes to develop OSA or may aggravate OSA in those who already have the condition.

Does treating OSA have glycaemic and other benefits?

The links between OSA and diabetes suggest that treatment of OSA might have glycaemic and other benefits beyond controlling OSA symptoms. Some observational studies have reported that treatment of OSA with continuous positive airways pressure (CPAP) was associated with improvements in glycaemia in people with

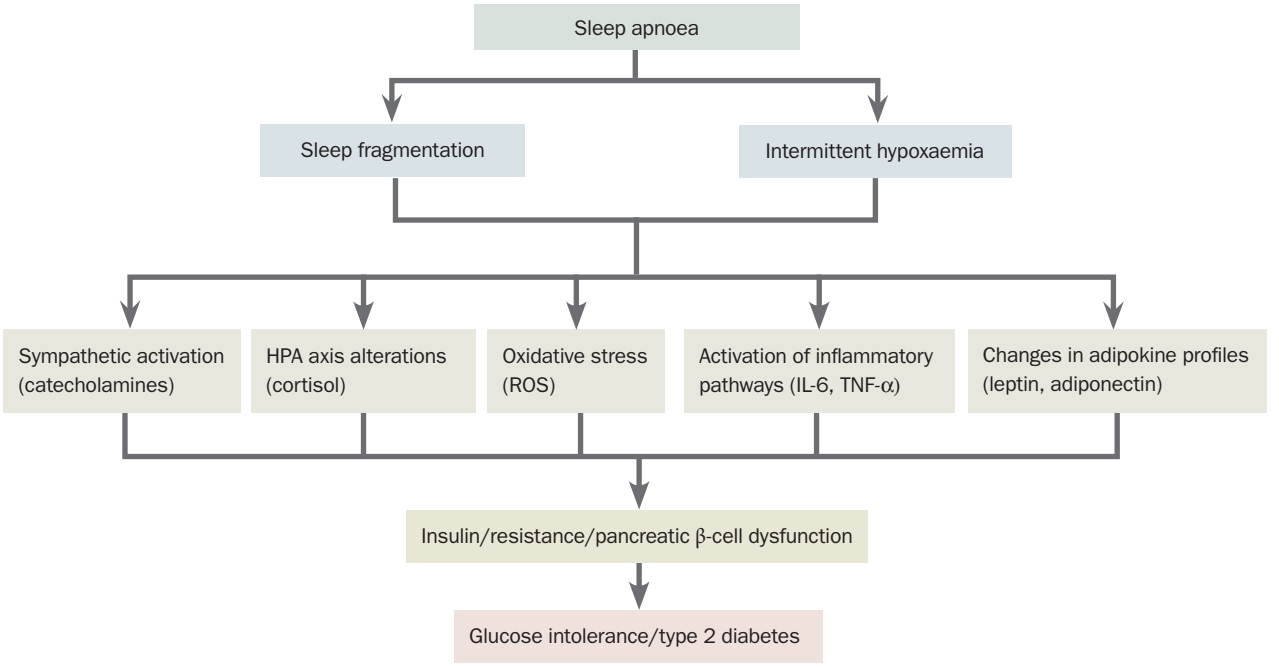

Figure. Potential mechanisms linking sleep apnoea to glucose intolerance.[1]

Abbreviations: HPA = hypothalamic–pituitary–adrenal; IL = interleukin; ROS = reactive oxygen species; TNF = tumour necrosis factor.

diabetes,[25,26] whereas other studies including randomised controlled trials showed no benefit of CPAP therapy on glycaemic control or insulin resistance.[27,28]

Recently, two meta-analyses revealed that CPAP treatment did not alter HbA_{1c} levels but were suggestive of an improvement in insulin resistance.[29,30] By contrast, a case-control study assessed clinical outcomes of using CPAP to manage OSA in patients with diabetes over periods as long as five years and reported a significant reduction in HbA_{1c} of 3.9% in the CPAP treatment group, compared with the control group.[31] However, this case-control design is much less reliable than a randomised controlled trial, and it therefore remains uncertain whether treatment of OSA with CPAP improves glucose metabolism. Nevertheless, there is some evidence to support the hypothesis that the degree of obesity and the amount of CPAP use may be important factors in the metabolic response to CPAP.[32]

Is OSA a reversible cardiovascular risk factor?

OSA and diabetes have both been linked to an increased risk of cardiovascular disease. Although CPAP treatment has been shown to have mixed results on glucose metabolism, it has been shown to have an impact on cardiovascular disease. Many observational studies suggest that CPAP improves survival and cardiovascular outcomes.[33,34] A 10-year observational study of the effect of CPAP treatment on cardiovascular outcomes showed that severe OSA in men significantly increased the risk of fatal and nonfatal cardiovascular events and CPAP treatment reduced this risk.[35] However, formal long-term randomised controlled trials are still needed to provide strong evidence.

Several large outcome-based trials are currently underway, which may provide valuable clarification about whether OSA is a reversible cardiovascular risk factor. The association between OSA and hypertension is better established.[36,37] Untreated OSA has been associated with an increasing risk of developing hypertension,[3,38] and treatment of OSA with CPAP has been shown to lead to reductions in mean systemic blood pressure measured over 24 hours, although these falls are small (about 2 to 3 mmHg), with the greatest benefit seen in patients with more severe OSA.[39] Therefore, physicians should also assess for the possibility of OSA in patients with resistant hypertension.[40] It should be noted, however, that the evidence for a blood pressure benefit has not been specifically demonstrated in people with diabetes.

Treatment recommendations

Weight loss should be the primary treatment strategy for both OSA and diabetes in people who are overweight or obese. Losing weight may improve energy and social interaction, reduce daytime fatigue, improve OSA, and achieve better control of blood glucose levels and blood pressure. The Sleep AHEAD study found that weight loss by intensive lifestyle intervention produced significant improvements in OSA severity in obese patients with diabetes,[41] which was maintained at four years despite a 50% weight regain over that period.[42] The converse of this is that physicians should be alert to

the possibility that drugs causing weight gain (e.g. insulin) could exacerbate OSA.

CPAP is indicated for treating the more severe and symptomatic end of the sleep apnoea spectrum. As described above, although there is no clear trial evidence that CPAP treatment has positive effects on glucose control, it has been consistently demonstrated to have beneficial effects on quality of life and blood pressure control. It also reduces fatigue and daytime sleepiness and consequently reduces risks of driving-related and workplace accidents.

Screening recommendations

Screening people with OSA for disorders of glucose metabolism

The International Diabetes Federation recommends that healthcare professionals monitor people with OSA for metabolic parameters, including waist circumference, blood pressure, fasting lipid levels and blood glucose levels (followed with a glucose tolerance test if necessary).[1]

Screening people with diabetes for OSA

There is not enough evidence to support screening for OSA in all people with diabetes. Furthermore, acceptance of CPAP treatment in people with minimal or no symptoms of OSA is relatively poor. Therefore, the International Diabetes Federation recommends a practical approach, which is to investigate patients with classic symptoms such as witnessed apnoeas, heavy snoring or daytime sleepiness. Due to the beneficial effect of OSA treatment on blood pressure, people with diabetes and refractory hypertension should also be screened for OSA.[1]

Polysomnography is the 'gold standard' for a diagnosis of OSA. However, it is expensive and not always available, especially in regional and remote areas. The International Diabetes Federation recommends a screening strategy using a two-stage approach in which a structured questionnaire (e.g. The Berlin questionnaire and OSA-50)[43] is used in the first stage to assess the probability of sleep apnoea. It should be noted that snoring and witnessed apnoeas may not be reported in people sleeping alone, and that the presence of other features of the metabolic syndrome, nocturia[44] or cardiovascular disease may help to indicate risk for OSA. Patients at high risk should either be referred for polysomnography or undergo a second stage, with an overnight evaluation at home with pulse oximetry or portable monitoring. However, a negative test with portable monitoring cannot completely rule out OSA. Patients who have a high probability of OSA but a negative test on portable monitoring may need further investigation by polysomnography.[1]

Conclusion

OSA and diabetes are both common conditions, and many studies have suggested that the presence of one condition increases the risk of the other. Emerging evidence strongly supports the links between the two conditions, but a causal link still remains to be determined.

Weight loss can improve both OSA and glucose control, and thus should be recommended systematically to all overweight patients with OSA and/or diabetes. There is still debate about whether treatment of OSA with CPAP can improve glucose metabolism. However, the benefits of CPAP treatment in people with OSA have been established in improvements in quality of life and blood pressure control. Furthermore, a patient presenting with one condition should be actively considered, and screened if appropriate, for the other condition. **ET**

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A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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