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CME ARTICLE

Obstructive sleep apnoea and Type 2 diabetes mellitus: are they connected?

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Mr Lim visited your clinic with his wife for his regular review for Type 2 diabetes mellitus and poorly controlled hypertension. He was taking four types of antihypertensive medications and his latest blood pressure reading was 160/90 mmHg. Mrs Lim casually asked if anything could be done about her husband's loud snoring with periodic loud coughing and choking noises, which was disturbing her sleep. Mr Lim reported that he was having headaches in the early morning and felt unrefreshed when waking up, although he slept for eight hours every night. He also said that he was gaining weight, but was unable to find the energy to exercise.

WHAT ARE OBSTRUCTIVE SLEEP APNOEA AND TYPE 2 DIABETES MELLITUS?

Obstructive sleep apnoea (OSA) is a sleep-related breathing condition that is characterised by episodes of complete or partial upper airway obstruction during sleep, leading to repetitive oxygen desaturation and sleep fragmentation. The diagnosis of OSA is made on polysomnography (also known as a sleep study) when the apnoea-hypopnea index (AHI) is ≥ 5/hr, together with the presence of symptoms or signs such as witnessed habitual snoring, nocturnal gasping or choking events, excessive daytime sleepiness, unrefreshing sleep, hypertension, congestive heart failure or AHI ≥ 15/hr without symptoms.[1] Severe OSA is defined as having AHI > 30/hr.

Type 2 diabetes mellitus (DM) is a common chronic disorder of glucose metabolism that mostly affects adults, although a younger age of onset can occur as well. Classical symptoms include polydipsia, polyuria, weight loss, fatigue and recurrent infections. The diagnosis of DM can be made through blood investigations, such as a fasting glucose level ≥ 7.0 mmol/L, a random glucose level of 11.1 mmol/L associated with typical symptoms of DM, or an oral glucose tolerance test.[2]

WHAT IS THE RELATIONSHIP BETWEEN OSA AND TYPE 2 DM?

Epidemiological evidence has demonstrated a high prevalence of OSA in patients with Type 2 DM. In a cross-sectional study, up to 23% of a diabetic population were found to have OSA.[3] In another study by Einhorn et al, 48% of diabetic patients had OSA with AHI ≥ 10/hr.[4] Conversely, studies have also indicated a high prevalence of DM or insulin resistance in OSA patients. In a large clinic-based cross-sectional study, 30.1% of OSA patients had Type 2 DM, while 20% had impaired glucose tolerance.[5] Additionally, a recent meta-analysis of prospective studies has found that moderate-to-severe OSA was associated with an increased incidence of Type 2 DM.[6]

Research has also suggested that OSA worsens DM control and may contribute to DM-related complications. In a study by Aronsohn et al, a higher severity of OSA was associated with poorer glycaemic control in DM patients, as measured by their glycated haemoglobin (HbA1c) levels; this result was independent of confounders such as body mass index, race, age, gender and number of years with DM.[7] A recent meta-analysis suggested that the presence of OSA may be associated with a greater severity of DM retinopathy, but the overall data remained mixed.[8] Conversely, data on the impact of DM on OSA severity is lacking.

The existence of a link between OSA and Type 2 DM would be unsurprising. These conditions share common risk factors such as obesity and age, which are also risk factors for cardiovascular disease. Obesity, in particular, is a prominent common risk factor. A 10% increase in weight has been shown to cause a six-fold increase in the risk of developing OSA.[9] In an early epidemiological study by Ford et al of more than 8,000 adults in the United States, a weight gain of 5 kg or more significantly increased the risk of developing DM.[10] OSA patients are also at increased risk of heart failure,[11] coronary artery disease,[12] arrhythmias[13] and sudden death,[14] while the macrovascular complications of DM, including ischaemic heart disease, are well known.

Possible mechanisms behind the link

The pathophysiological links between OSA and DM have yet to be fully elucidated. Studies have suggested that an important

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mechanism is intermittent hypoxia, which occurs in OSA. Intermittent hypoxia enhances sympathetic activity and drives oxidative stress and chronic inflammation; these likely contribute to derangements in glucose metabolism. The injurious effect of hypoxia may also directly affect pancreatic beta cell, liver and adipose tissue function, all of which are involved in glucose homeostasis. The sleep fragmentation and sleep deprivation associated with OSA may have an additive, adverse impact on insulin sensitivity, due to the mechanism of sympathetic activation, as well as alterations in growth hormone and cortisol secretion.[15]

HOW RELEVANT IS THIS TO MY PRACTICE?

High prevalence

OSA and DM are common and worsening global health problems. The prevalence of OSA was shown to have increased from 14% to 55% over the past two decades, according to a large community cohort study based in the United States.[16] Recent data from the Singapore Health Study estimated that 18.1% of Singapore's population have sleep apnoea associated with significant daytime sleepiness.[17] The estimated prevalence of moderate-to-severe sleep apnoea (AHI ≥ 15/hr) was also at a high of 30.5%.[17] The local prevalence of DM was already 12.3% in 2013.[18] As obesity is a risk factor for both OSA and DM, the prevalence of both conditions appears set to rise further in the face of the worsening obesity epidemic.[19] By 2040, 642 million of the world's population are projected to be living with DM.[20]

Association with multiple significant comorbidities

Apart from the cardiovascular conditions mentioned above, OSA is strongly associated with hypertension and has been identified in one study to be the most common secondary cause of drug-resistant hypertension.[21] OSA has also been associated with hypertensive patients who are 'non-dippers' at night.[22] Other comorbidities that have been linked to OSA include stroke, depression, cognitive impairment, decreased quality of life, and psychological and social function.[23] DM is a chronic debilitating medical disease with multiple complications. These include macrovascular complications of stroke, ischaemic heart disease, peripheral vascular disease, and microvascular complications of neuropathy, nephropathy and retinopathy. DM has also been associated with depression and decreased work productivity. Consequently, it is a disease that poses a significant socioeconomic burden.[24]

WHAT IS THE STANDARD TREATMENT FOR OSA?

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) is the standard treatment for OSA. CPAP treatment applies a positive pressure to the airway with the aim of splinting open the collapsible airway, thereby obliterating the repetitive airway obstruction and oxygen desaturation that occur in OSA.[25] The treatment uses a CPAP machine, which contains a motor that generates a positive pressure, and a nasal or oronasal mask that is strapped to the patient's face, as well as tubing that connects the machine and mask. Patient acceptance of CPAP treatment and adherence to it remain a challenge. Reasons cited include treatment inconvenience and side effects such as mask discomfort, pressure intolerance and dryness of the upper airways. However, these side effects are often minor and can be adequately addressed at follow-up.

Indications for CPAP treatment in DM patients are the same as those in general OSA patients. CPAP treatment should be offered to all patients with symptomatic OSA or moderate-to-severe OSA (AHI ≥ 15/hr) without symptoms.[26] Evidence is lacking for treatment benefits in patients with mild OSA who are asymptomatic. The most significant benefit of CPAP for OSA treatment is improvement of daytime sleepiness, daytime function and quality of life.[27] A previous meta-analysis showed that CPAP only decreased 24-hour mean blood pressure (BP) by approximately 2 mmHg.[28] However, a recent study reported that the magnitude of BP reduction was demonstrated to be greater in a subgroup of OSA patients with drug-resistant hypertension.[29] Nevertheless, the BP reduction through CPAP is inferior to that produced by antihypertensive medication, and optimal antihypertensive pharmacotherapy remains paramount. Several studies have also suggested that CPAP can mitigate the adverse cardiovascular risks and mortality outcomes associated with OSA.[29,30]

Weight management

Weight management plays an important role in the holistic management of the obese OSA patient. This can be achieved through dietary and lifestyle modifications, or bariatric surgery in a highly selected patient group.

Does CPAP improve DM?

While there is great interest in the question of whether CPAP treatment improves DM, the data has, unfortunately, been mixed. Two recent meta-analyses, which included non-randomised trials as well as trials with non-diabetic and diabetic OSA patients, demonstrated that CPAP treatment improved insulin sensitivity.[31,32] However, in the only randomised controlled trial by West et al, which specifically evaluated the impact of CPAP treatment on glycaemic control in known Type 2 diabetic patients with newly diagnosed OSA, three months of CPAP intervention did not reveal any significant benefit for insulin resistance or HbA1c.[33]

It is possible that longer durations of CPAP usage per night may be required to achieve improvements in glycaemic control. One limitation of West et al's study was that average CPAP usage in the treatment arm was less than four hours.[33] A recent study by Grimaldi et al found that poor glycaemic control was associated with the frequency of obstructive respiratory events during rapid eye movement (REM) sleep, but not non-REM sleep.[34] As REM sleep predominates in the latter part of the sleep period, the majority of the REM sleep period would have been left untreated in patients who only had four hours of CPAP.

In summary, there is strong epidemiological and pathophysiological evidence supporting the association between OSA and DM. The mechanism by which OSA impacts glucose homeostasis has yet to be fully elucidated, but multiple pathways are likely to play a role. It is hoped that further research would be able to identify more specific pathophysiological pathways between the two diseases that may guide us in both the timing and nature of interventions to improve patient outcomes. Ultimately, it should be emphasised that diabetic medications are still the mainstay of treatment to achieve optimal glycaemic control, together with lifestyle modification and weight loss.

WHO SHOULD BE REFERRED FOR SLEEP STUDIES?

Currently, there is still a lack of evidence to support the benefits of screening every diabetic patient for OSA. Diabetic patients with symptoms suggestive of OSA (e.g. snoring with unrefreshed sleep and significant daytime sleepiness) should be referred to a sleep specialist for further evaluation.[35] Validated questionnaires, such as the Berlin questionnaire and STOP-Bang questionnaire, may be used to aid in patient evaluation, although they have their limitations.[36]

TAKE HOME MESSAGES

1. OSA and Type 2 DM are highly prevalent and share common risk factors, with obesity being the most prominent. Complications related to OSA, Type 2 DM and obesity often overlap.
2. Intermittent hypoxia and sleep fragmentation in OSA may affect glucose metabolism and insulin sensitivity.
3. There is currently a lack of evidence to support the benefits of screening every DM patient for OSA.
4. DM patients with symptoms suggestive of OSA may be referred to a sleep specialist for further evaluation.
5. CPAP remains the standard treatment for OSA and should be offered to all symptomatic patients.
6. Limited evidence suggests that CPAP treatment may improve glycaemic control.
7. Diabetic medications, together with lifestyle modifications and weight loss, remain the mainstay of treatment to achieve optimal DM control.
8. Further research is necessary to clarify the pathophysiological mechanisms and develop treatment strategies for patients with both DM and OSA.

You referred Mr Lim to a sleep specialist and a sleep study was performed. It confirmed your suspicion of OSA. Ever since Mr Lim had started using a CPAP device at night, he felt more refreshed after waking up. He was able to go on daily brisk walks, and his weight and blood pressure gradually improved after subsequent visits to your clinic. He also said that his wife was sleeping better.

ABSTRACT Obstructive sleep apnoea (OSA), a sleep-related breathing condition, is diagnosed based on a patient's apnoea-hypopnea index from a sleep study, and the presence or absence of symptoms. Diabetes mellitus (DM) and OSA share a significant common risk factor, obesity, with all three conditions contributing to the risk of developing cardiovascular diseases. The pathophysiological links between OSA and DM are still unclear, but intermittent hypoxia may be an important mechanism. More awareness of the possible link between OSA and DM is needed, given their increasing prevalence locally and worldwide. Continuous positive airway pressure is the standard treatment for OSA, while weight loss through dietary and lifestyle modifications is important to holistically manage patients with either condition. There is currently insufficient evidence to support the benefits of screening every diabetic patient for OSA. However, diabetic patients with symptoms suggestive of OSA should be referred to a sleep specialist for further evaluation.

Keywords: diabetes mellitus, obstructive sleep apnoea, sleep-disordered breathing

REFERENCES

1. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest 2014; 146:1387-94.
2. Ministry of Health, Singapore. Diabetes Mellitus. In: Clinical Practice Guidelines (Medical) 2014 [online]. Available at: https://www.moh.gov.sg/content/moh_web/healthprofessionalsportal/doctors/guidelines/cpg_medical/2014/cpgmed_diabetes_mellitus.html. Accessed February 4, 2017.
3. West SD, Nicoll DJ, Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. Thorax 2006; 61:945-50.
4. Einhorn D, Stewart DA, Erman MK, et al. Prevalence of sleep apnea in a population of adults with type 2 diabetes mellitus. Endocr Prac 2007; 13:355-62.
5. Meslier N, Gagnadoux F, Giraud P, et al. Impaired glucose-insulin metabolism in males with obstructive sleep apnoea syndrome. Eur Respir J 2003; 22:156-60.
6. Wang X, Bi Y, Zhang Q, Pan F. Obstructive sleep apnoea and the risk of type 2 diabetes: a meta-analysis of prospective cohort studies. Respirology 2013; 18:140-6.
7. Aronsohn RS, Whitmore H, Van Cauter E, Tasali E. Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. Am J Respir Crit Care Med 2010; 181:507-13.
8. Leong WB, Jadhakhan F, Taheri S, et al. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. Diabet Med 2016; 33:158-68.
9. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA 2000; 284:3015-21.
10. Ford ES, Williamson DF, Liu S. Weight change and diabetes incidence: findings from a national cohort of US adults. Am J Epidemiol 1997; 146:214-22.
11. Gottlieb DJ, Yenokyan G, Newman AB, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation 2010; 122:352-60.
12. Peker Y, Carlson J, Hedner J. Increased incidence of coronary artery disease in sleep apnoea: a long-term follow-up. Eur Respir J 2006; 28:596-602.
13. Mehra R, Benjamin EJ, Shahar E, et al; Sleep Heart Health Study. Association of nocturnal arrhythmias with sleep-disordered breathing: The Sleep Heart Health Study. Am J Respir Crit Care Med 2006; 173:910-6.
14. Gami AS, Howard DE, Olson EJ, Somers VK. Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 2005; 352:1206-14.
15. Kent BD, McNicholas WT, Ryan S. Insulin resistance, glucose intolerance and diabetes mellitus in obstructive sleep apnoea. J Thorac Dis 2015; 7:1343-57.

16. Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol 2013; 177:1006-14.
17. Tan A, Cheung YY, Yin J, et al. Prevalence of sleep-disordered breathing in a multiethnic Asian population in Singapore: A community-based study. Respirology 2016; 21:943-50.
18. International Diabetes Federation. Extract of the Global Diabetes Scorecard Tracking Progress for Action [online]. Available at: http://www.idf.org/sites/default/files/attachments/Singapore_Scorecard.pdf. Accessed December 19, 2016.
19. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999-2010. JAMA 2012; 307:491-7.
20. International Diabetes Federation. Diabetes: facts and figures [online]. Available at: http://www.idf.org/about-diabetes/facts-figures. Accessed February 4, 2017.
21. Pedrosa RP, Drager LF, Gonzaga CC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension 2011; 58:811-7.
22. Portaluppi F, Provini F, Cortelli P, et al. Undiagnosed sleep-disordered breathing among male nondippers with essential hypertension. J Hypertens 1997; 15:1227-33.
23. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. Lancet 2014; 383:736-47.
24. Ettaro L, Songer TJ, Zhang P, Engelgau MM. Cost-of-illness studies in diabetes mellitus. Pharmacoeconomics 2004; 22:149-64.
25. Sullivan CE, Issa FG, Berthon-Jones M, Eves L. Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. Lancet 1981; 1:862-5.
26. Epstein LJ, Kristo D, Strollo PJ Jr, et al; Adult Obstructive Sleep Apnea Task Force of the American Academy of Sleep Medicine. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med 2009; 5:263-76.
27. Patel SR, White DP, Malhotra A, Stanchina ML, Ayas NT. Continuous positive airway pressure therapy for treating sleepiness in a diverse population with obstructive sleep apnea: results of a meta-analysis. Arch Intern Med 2003; 163:565-71.
28. Haentjens P, Van Meerhaeghe A, Moscariello A, et al. The impact of continuous positive airway pressure on blood pressure in patients with obstructive sleep apnea syndrome: evidence from a meta-analysis of placebo-controlled randomized trials. Arch Intern Med 2007; 167:757-64.
29. Martínez-Garcia MA, Capote F, Campos-Rodriguez F, et al; Spanish Sleep Network. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013; 310:2407-15.
30. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005; 365:1046-53.
31. Iftikhar IH, Khan MF, Das A, Magalang UJ. Meta-analysis: continuous positive airway pressure improves insulin resistance in patients with sleep apnea without diabetes. Ann Am Thorac Soc 2013; 10:115-20.
32. Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath 2013; 17:33-8.
33. West SD, Nicoll DJ, Wallace TM, Matthews DR, Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. Thorax 2007; 62:969-74.
34. Grimaldi D, Beccuti G, Touma C, Van Cauter E, Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. Diabetes Care 2014; 37:355-63.
35. How CH, Hsu PP, Tan KL. Recognising sleep apnoea. Singapore Med J 2015; 56:129-32; quiz 144.
36. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. Can J Anaesth 2010; 57:423-38.

SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME

(Code SMJ 201704A)

		True	False
1.	Obstructive sleep apnoea (OSA) is a sleep-related breathing condition characterised by episodes of complete or partial upper airway obstruction during sleep, leading to repetitive oxygen desaturation and sleep fragmentation.	☐	☐
2.	The presence of symptoms or signs such as witnessed habitual snoring, excessive daytime sleepiness, unrefreshing sleep and hypertension is absolutely necessary to make a diagnosis of OSA.	☐	☐
3.	An apnoea-hypopnea index of ≥ 5/hr without symptoms from a sleep study can be used to diagnose OSA.	☐	☐
4.	As much as 30.1% of OSA patients had Type 2 diabetes mellitus (DM), while up to 20% had impaired glucose tolerance in an epidemiological study.	☐	☐
5.	A meta-analysis of prospective studies found that mild-to-moderate OSA was associated with an increased incidence of Type 2 DM.	☐	☐
6.	OSA may worsen DM control and contribute to DM-related complications.	☐	☐
7.	Hypertension is a prominent common risk factor for DM and OSA.	☐	☐
8.	Side effects of continuous positive airway pressure (CPAP) treatment are usually minor and can be adequately addressed.	☐	☐
9.	Intermittent hypoxia has been suggested to be a pathophysiological link between OSA and DM.	☐	☐
10.	OSA prevalence was shown to have increased from 14% to 55% over the past two decades in a United States community study.	☐	☐
11.	The local prevalence of DM was found to be 12.3% in 2013.	☐	☐
12.	OSA is associated with hypertension, stroke, depression and cognitive impairment.	☐	☐
13.	OSA has been identified to be the most common cause of primary drug-resistant hypertension in one study.	☐	☐
14.	CPAP is the standard treatment for OSA.	☐	☐
15.	CPAP treatment should be offered to all patients with OSA.	☐	☐
16.	Blood pressure reduction through CPAP treatment is comparable to that produced by pharmacotherapy.	☐	☐
17.	Weight management through dietary and lifestyle modifications plays an important role in the holistic management of the obese OSA patient.	☐	☐
18.	Poor glycaemic control was found to be associated with the frequency of obstructive respiratory events during rapid eye movement sleep.	☐	☐
19.	There is strong evidence that CPAP treatment improves glycaemic control in Type 2 DM.	☐	☐
20.	Evidence suggests that screening all diabetic patients for OSA using validated questionnaires is beneficial.	☐	☐

Doctor's particulars:

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