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Narrative Review: Obesity, Type 2 DM and Obstructive Sleep Apnoea—Common Bedfellows

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Abstract: Obstructive sleep apnoea (OSA) and type 2 DM mellitus (T2DM) share obesity as a major risk factor. Furthermore, these conditions share overlapping mechanisms including inflammation, activation of the autonomic nervous system, and hypoxia-linked endocrinopathy. Hence, the pathogenesis of the two conditions may be more closely related than previously recognised. This raises the question of whether treatment of OSA might assist resolution of obesity and/or T2DM. Here, we present a narrative review of the literature to identify clinical and scientific data on the relationship between obstructive sleep apnoea and T2DM control. We found there is a paucity of adequately powered well-controlled clinical trials to directly test for a causal association. While routine screening of all T2DM patients with polysomnography cannot currently be justified, given the high prevalence of sleep disordered breathing in the overweight/obese population, all T2DM patients should at a minimum have a clinical assessment of potential obstructive sleep apnoea risk as part of their routine clinical care. In particular, screening questionnaires can be used to identify T2DM subjects at higher risk of OSA for consideration of formal polysomnography studies. Due to morbid obesity being a common feature in both T2DM and OSA, polysomnography should be considered as a screening tool in such high-risk individuals.

Keywords: obstructive sleep apnoea; DM; obesity; inflammation; polysomnography



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1. Introduction

An overlap in morphological and metabolic features in patients with obstructive sleep apnoea (OSA) and type 2 DM mellitus (T2DM) has been recognised and described since 1993 [1–3], with most patients with T2DM being overweight or obese with excessive visceral fat, features commonly seen in OSA. T2DM is characterised by insulin resistance with relative insulin deficiency and accounts for 90–95% of the total DM population [4]. It is a chronic progressive condition associated with both microvascular and macrovascular complications resulting in high morbidity and mortality. The global incidence of DM has been rising rapidly in parallel with the increasing prevalence of obesity. Recent studies have shown DM to affect 537 million people (<https://DMAtlas.org/> accessed 14 July 2022). A recent study showed that the prevalence of overweight and obese children combined between 1980 and 2013 rose by 47.1%, with the total number of overweight and obese children and adults increasing from 857 million in 1980 to 2.1 billion globally in 2013 [5].

OSA is a multi-system disorder, affecting cardiovascular and neuro-endocrine systems and lipid metabolism. OSA affects between 20 and 25% of adult men in some populations and its incidence rises with obesity [6], a concerning fact given that over 37% of the world population is currently classed as obese (BMI > 30 kg/m²) [5]. OSA is characterised by repetitive episodes of hypoxia and hyper-oxygenation with sleep fragmentation. Various

mechanisms contribute to the sequelae of OSA including fragmented sleep and loss of sleep, activation of the sympathetic nervous system, recurrent intermittent hypoxia, endothelial dysfunction, systemic inflammation, and hormonal imbalance. The prevalence of OSA (defined as Apnoea–Hypopnea Index(AHI) > 5/hr) is influenced by gender and age, with males and postmenopausal women at highest risk. Evidence of an association between T2DM and OSA is mounting, raising questions as to whether there might be a causal relationship in either direction. A clearer understanding of the pathophysiological pathways and interrelationships between T2DM and OSA may help target common mechanisms and improve outcomes in these patients. In this review, we summarise evidence for possible causal associations between OSA and T2DM and address several practical questions, namely, does treatment of OSA improve diabetic control, does improved DM control improve OSA and should all patients with T2DM be routinely screened for OSA?

2. Potential Pathophysiological Links between T2DM and OSA

2.1. Inflammation

A model for the common origins of OSA and T2DM is presented in Figure 1. Increased inflammatory markers are seen in both T2DM and OSA, thereby suggesting that low-grade inflammation may be a possible link between the two conditions. Patients with T2DM have increased inflammatory markers including serum levels of fibrinogen, C-reactive protein (CRP), and IL-6 [7], with raised serum CRP and TNF α also reported in OSA [8–11]. Inflammatory cytokines can impair glucose metabolism with TNF α , conferring insulin resistance in animal studies via impairment of insulin receptor function [12,13]. TNF α also acts on adipocytes through transcription factors such as NF- κ B and hypoxia-inducible factor-1 [14]. The concept of oxidative stress characterised by an imbalance between oxidant-producing systems and antioxidant defence mechanisms (redox balance), resulting in excessive formation of reactive oxygen species (ROS), is well documented in OSA [15]. Chronic repetitive hypoxic episodes increase the formation of ROS and cytokines, suppressing insulin secretion and worsening insulin sensitivity [16–18]. ROS can contribute to dysregulation of adipo-cytokines, thereby increasing insulin resistance. Moreover, some cytokines have sleep regulatory properties with TNF α , IL-6, and IL-1 promoting NREM sleep, whereas IL-1 antagonists inhibit NREM sleep [18,19]. Inflammation may lead to increased production of advanced glycation end-products (AGE) from oxidation and glycation of reducing sugars and amino acids [20]. High levels of AGEs have been detected in both T2DM and non-diabetic patients with OSA [21]. These compounds may play a role in diabetic vascular disease [22]. In non-diabetic patients with OSA, levels of AGEs were significantly higher than those without OSA and positively correlated with an AHI \geq 5/h, while there was no relationship with measures of insulin sensitivity [23]. In 18 patients in this cohort with moderate to severe OSA treated with CPAP, there was a significant decrease in AGEs from 5.1 to 4.9 ($p = 0.017$) after 3 months of treatment. Nonetheless, the role of AGEs in the pathophysiology of OSA and DM requires further study. Sleep deprived obese patients with OSA were observed to have higher levels of pro-inflammatory markers (IL-2, IL-4, IL-5, IL-6, IL-8, IL-13, and IFN- γ) in OSA subjects compared to controls without OSA [24].

2.2. Autonomic Nervous System

Increased sympathetic activity may lead to altered glucose metabolism in OSA. Sympathetic activity increases muscle glycogen breakdown and hepatic gluconeogenesis. Activation of the sympathetic nervous system with catecholamine release may raise cholesterol, triglycerides, and insulin and cause glucose intolerance and insulin resistance through lipolysis [25,26]. Insulin resistance is aggravated by increased lipolysis and raised levels of free fatty acids [27].

2.3. Endocrinopathy

Several hormones have been identified in the development of insulin resistance and DM in OSA. In animal studies, leptin-deficient mice exposed to hypoxic environments were observed to develop elevated insulin levels and impaired glucose tolerance [28]. The same observation was replicated in non-obese mice exposed to intermittent hypoxia (IH) under euglycemic environment with reduction in insulin sensitivity and reduced muscle glucose uptake despite pharmacologic blockade of the sympathetic system [29,30]. A study of glucose-induced insulin secretion and gene expression showed that IH reduced β -cell insulin secretion, potentially through downregulation of CD38 [31], with the ectocyclase activity of CD38 to produce intracellular cyclic ADP-ribose being critical for insulin secretion [32].

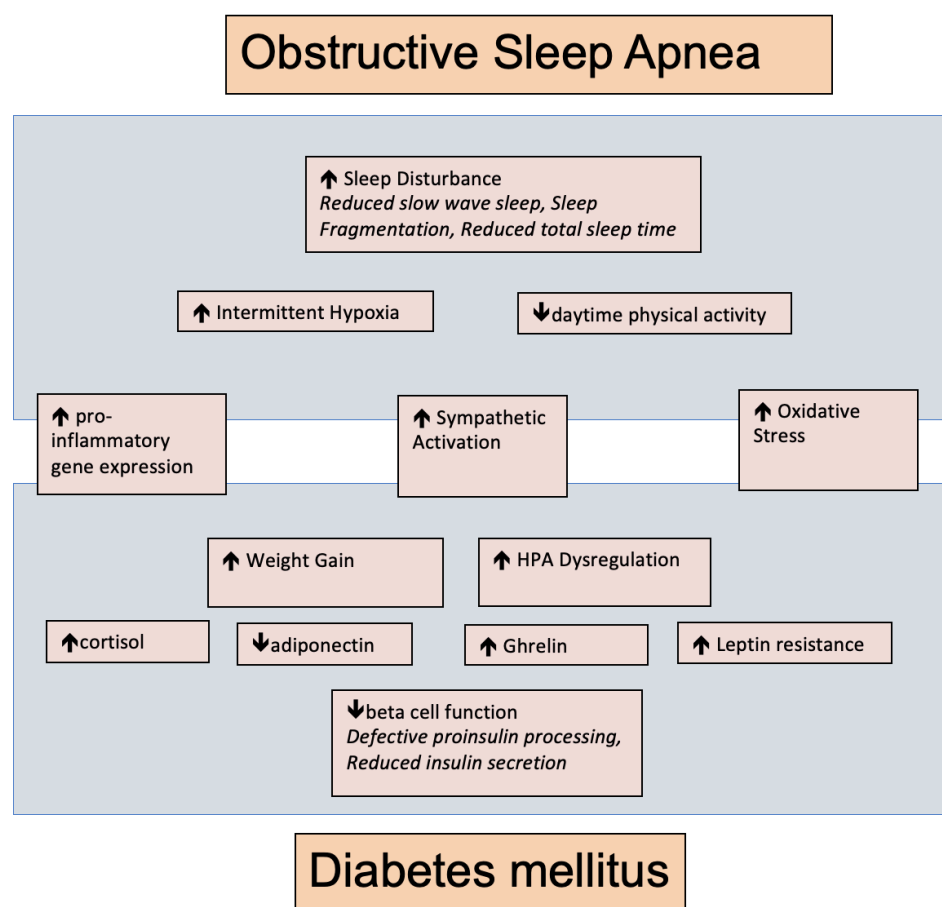


Figure 1. This figure depicts the many disordered pathways observed in OSA and DM and the potential important links between them. Up and down arrows indicate increases or decreases in the relevant condition/marker in either OSA (top grey panel) or DM (bottom grey panel) or both (pink boxes linking the two grey panels).

Adipose tissue is not only an energy storage tissue but an active endocrine organ secreting adipokines including leptin, adiponectin, and cytokines [14,33,34]. Leptin is secreted by white adipocytes and acts as an appetite suppressant at the hypothalamic level as well as acting peripherally through skeletal muscles and pancreatic B cells [35–37]. Levels of leptin in some studies correlate with the percentage of body fat and have been observed to be higher in obese patients suggesting leptin resistance [38,39]. Leptin is not only involved in regulation of insulin secretion and glucose metabolism but has a role in the regulation of both the sympathetic system and inflammatory responses [18]. Leptin has been implicated in ventilatory control. Hypercapnic obese and non-obese patients have been found to have high levels of leptin, which improved with non-invasive ventilation,

particularly in patients with obesity hypoventilation syndrome [40–43]. High leptin levels are associated with reduced ventilatory drive, regardless of the amount of body fat in some studies [44]. Nocturnal awakening and arousals are associated with altered levels of leptin, leptin resistance, pulsatile cortisol release, and autonomic activation, which can lead to dysregulation of the hypothalamic–pituitary–adrenal axis and glucose impairment fostering the development of T2DM [45]. Leptin was also found to be elevated in OSA due to repeated episodes of hypoxia. Therefore, it remains unresolved as to whether leptin elevation is a result of sleep disordered breathing or the cause of it. Reduced circulating leptin levels were detected after treatment with CPAP, particularly in non-obese patients [46–48]. However, some studies have found no relationship between leptin and AHI after adjustments for obesity [49,50].

Adiponectin increases fatty acid metabolism and inhibits gluconeogenesis in the liver [51]. Levels are reduced in insulin resistance, DM, and visceral obesity among other conditions [52,53]. The relationship between adiponectin and OSA remains unresolved. Levels of adiponectin are significantly reduced in OSA patients compared to simple snorers, but other studies have reported no difference [54,55]. CPAP therapy reduced adiponectin levels after only two days of treatment in one study, whereas in a randomised trial, no change was observed between subjects treated with CPAP and sham CPAP after 3 months of treatment [56,57]. Compliance with CPAP was a compounding effect in previous studies on the effect of CPAP on hormonal changes.

Glucagon-like peptide (GLP)-1 receptor agonist therapy is highly effective for weight loss and glycaemic control in T2DM and has similarly been shown to have positive benefits for OSA [58,59]. Severe OSA has been shown to be associated with a lower GLP-1 response to glucose challenge, which could be yet another mechanism by which OSA affects glucose metabolism.

2.4. Pancreatic Effects of Chronic Intermittent Hypoxia

Examination of a possible association between DM and OSA cannot avoid addressing the role of the pancreas. Pancreatic endocrine dysfunction is central to the pathophysiology of DM, as while insulin resistance drives type 2 DM, it only when the pancreas no longer keep up with the demand for more insulin that hyperglycaemia eventuates. In studies of pancreatic β -cell function in rodents exposed to intermittent hypoxia (IH), impaired insulin synthesis was demonstrated, speculated to be due to reduced activity of the enzyme that converts pro-insulin to active insulin. β -cell apoptosis results from exposure to IH [60]. Sherwani et al. noted IH exposed mice had significantly higher plasma levels of glucose associated with lower insulin levels compared to animals exposed to intermittent air. IH resulted in reduced insulin release in addition to decreased islet cell viability thought to be mediated by increased release of long chain fatty acids such as palmitic and stearic acid [61]. Polak et al., showed in mice that even after discontinuation of IH, the impaired glucose metabolism persisted to varying degrees [62]. Reactive oxygen species (ROS) from mitochondria have also been implicated in the endocrinopathy with resultant β -cell injury following exposure to IH. This effect is mediated via downregulation of insulin secretion promoting genes such as CD38 [31,32].

3. Sleep Loss and Fragmentation

Sleep deprivation and short sleep are risk factors for impaired glucose metabolism and adverse cardiovascular events. Sleep fragmentation and reduced total sleep time in the absence of significant OSA independently increase the risk of T2DM [63]. Cappuccio et al. in 2010 in a systematic review and meta-analysis of over 100,000 patients assessed the relationship between sleep habits and incidence of DM. Quantity and quality of sleep predicted the risk of development of DM with sleep maintenance insomnia conferring the highest risk (RR was 1.84; 1.39–2.43, $p < 0.0001$) [64]. Xu et al. reported on the effect of day napping or short night sleeping and concluded that both conditions were associated with an increased risk of DM [65]. Sleep fragmentation results in reduced proportion of slow

wave sleep and increased sympathetic activity, both of which may adversely affect glucose metabolism. Selective suppression of slow wave sleep in healthy adults has been reported to reduce insulin sensitivity [66,67]. Two laboratory-based studies examined these concepts. One compared 4 and 12 h sleep and noted that the rate of clearance of glucose post-challenge was slower in the sleep restricted group, suggesting reduced sensitivity to insulin. The second crossover study compared 4 and 10 h in bed and demonstrated higher morning glucose levels in the sleep-deprived patients [68]. In an animal study, Gharib et al. observed that mice exposed to sleep fragmentation developed insulin resistance and impaired glucose metabolism through up-regulation of transcription factors and other pathways [69]. A study by Fendri et al. examined the overnight glucose profiles of patients with diagnosed T2DM who were being investigated for symptomatic sleep disordered breathing. All the patients had continuous glucose monitoring during polysomnography [70]. The mean nocturnal glucose level was 31% higher in the sleep apnoea patients ($p = 0.05$) and more marked during REM (38% greater, $p = 0.008$) compared to the non-sleep apnoea patients. In a study examining the effect of sleep duration on the risk of DM and preDM, excluding patients with high-risk features for OSA, Chao et al. found that both short and long sleepers (<6 h, ≥ 8.5 h) had higher risk of newly diagnosed DM with OR 1.55 (CI 1.07–2.24) and 2.83 (1.19–6.73), respectively [71]. No effect was observed with the pre-DM state. Similarly, insufficient and excessive sleep among obese adolescents was associated with acute and chronic glucose intolerance [72]. In a cohort of 96 obese sleep-deprived adolescents, 58 had sleep apnoea (RDI > 5 /h, portable overnight polysomnography) and 42% had abnormal glucose metabolism based on abnormal HOMA, fasting glucose levels, and OGTT; higher fasting levels of glucose were observed with higher severity of OSA, suggesting an interplay between disordered sleep, inflammation, and abnormal glucose metabolism.

4. Population Studies of Relationship between OSA and T2DM

Although many studies have established a causal link between obesity and T2DM, as well as between obesity and OSA, no clear association has been demonstrated between T2DM and OSA. The latter association has been implied by indirect observation studies, and there is still a significant knowledge gap in this area. A large-scale multi-ethnic study of adults demonstrated abnormal fasting glucose and T2DM was strongly associated with moderate–severe OSA [73]. Studies suggest 30% of all patients with OSA have T2DM and 86% of obese OSA patients have T2DM [74,75]. In the Sleep Health Heart Study, fasting and 2 h glucose levels were significantly higher in the moderate–severe OSA patients than those with no sleep-disordered breathing [75]. In the same study, nocturnal hypoxemia was independently associated with markers of impaired glucose metabolism [76]. Seicean et al. in their study of 2588 subjects with sleep-disordered breathing (RDI ≥ 10 , unattended polysomnography) found that OSA was associated with T2DM and impaired glucose tolerance with an adjusted odds ratio of 1.4 (1.1–2.7) for impaired fasting glucose and impaired glucose tolerance and 1.7 (1.1–2.7) for occult DM [77]. The Wisconsin Sleep Cohort Study OSA (AHI ≥ 15) reported similar results with a higher risk for T2DM after adjusting for age, sex, and waist girth [78]. Marshall et al. reported on a smaller population of 399 patients in Western Australia of whom 10 had moderate–severe OSA (RDI ≥ 15) and 2 (20%) had incident T2DM at 4 years [79]. A small prospective case–control study compared markers of glucose intolerance following a glucose load between young men with OSA to matched controls and found that OSA was associated with lower insulin sensitivity and higher total insulin secretion to maintain normoglycemia [80]. Bulcun et al., in a study of 112 patients with OSA and 12 snorers, found that glucose disorders were much higher in OSA patients than snorers (50.8% versus 15.7%; $p = 0.055$), and in addition observed significant positive correlations between insulin resistance and both AHI ($p = 0.005$) and arousal index ($p = 0.01$) [81]. In 137 patients with diagnosed T2DM and preDM with extreme obesity (BMI > 40 kg/m²), the ORs for associated OSA were 3.18 (95% CI; 1.00, 10.07) and 4.17 (CI; 1.09, 15.88), respectively, after adjustment for age, obesity, and insulin levels [82]. The European Sleep Apnoea Cohort Study demonstrated that for all levels of obesity, the presence of OSA increased the risk of T2DM and was associated

with worse glycaemic control [83]. Moreover, a metaanalysis of 25 studies covering 154,948 OSA patients showed an association between OSA and increased risk of impaired fasting glucose and T2DM development [84].

The Sleep AHEAD study showed that baseline apnoea–hypopnea index (AHI) and weight loss were the most important predictors of AHI change [85]. Notably, weight loss by diet or bariatric surgery has a positive effect both on OSA severity and diabetic control [86], indicating the central role that excess body adiposity plays in the pathogenesis of both conditions. Additional prospective studies are needed to better characterise the mechanistic relationship between T2DM and OSA.

5. Effect of CPAP on T2DM

CPAP treatment has been associated with improvement in insulin sensitivity, although clinical trials have revealed conflicting results. In general, most trials have been uncontrolled and un-blinded studies examining the effect of treatment of OSA with CPAP on markers of glucose metabolism. Various studies have identified improvement with use of CPAP in post-prandial glucose levels [87], hyperinsulinemic euglycemic clamp HbA1c, and mean sleep glucose levels [87–90]. However, outcomes from other studies on the effect of CPAP therapy on long-term glucose control in T2DM with OSA have not shown consistent benefit [57,91]. In eight randomised controlled trials (five with non-DM and three with DM), no significant difference was observed with CPAP on fasting glucose or HbA1c [92]. However, a retrospective analysis of patients with DM and OSA treated with CPAP showed a significant improvement in HbA1c after 5 years when compared with matched controls not receiving CPAP [93]. Moreover, a recent meta-analysis of seven trials of patients with DM and OSA treated with CPAP suggested improvement in glycaemic control and insulin resistance [94]. Nonetheless, there was considerable heterogeneity in the response to CPAP in these trials being considered.

The potential reasons for the disparity of these results are complex. The outcomes of CPAP therapy on OSA will depend on the effectiveness of treatment and compliance with therapy. Importantly, even with effective CPAP therapy, there may not be normalisation of all physiological parameters. Satisfactory compliance with CPAP is generally considered to require at least 4 h of treatment per night, though this figure is arbitrary [95]. Even with greater than 4 h use of CPAP per night, a significant number of patients still complain of daytime tiredness [96].

Nonetheless effective use of CPAP may improve some parameters. Steiropoulos et al. noted that only those subjects utilising CPAP for more than 4 h per night showed a decrease in HbA1c [97]. In the study by West et al., which did not demonstrate an effect on HbA1c, average compliance was only 3.6 h on 75% of nights per night [57]. In a study by Oktay et al., no effect of CPAP was observed on fasting blood glucose, although no measures of compliance were monitored [91]. The type of CPAP therapy does not appear to influence the outcome. No demonstrable benefit was identified when auto-titrating CPAP was compared to fixed pressure machines in treatment of sleep disordered breathing in diabetics [98]. In a recent publication, nightly eight-hour CPAP for 2 weeks resulted in improved glucose levels by 1276.9 mg/dL ($p = 0.03$) and improved insulin sensitivity compared to placebo in prediabetic patients [99].

The severity of OSA in these studies has been similar, on the basis of the Respiratory Disturbance index or AHI, although it should be recognised that these measures, which are widely used to categorise OSA, describe the frequency of respiratory events, but not the severity of such events. These are aggregate markers which include hypopneic and apnoeic events terminated by arousal and also those leading to hypoxemia. More recently, it has been recognised that there are different phenotypes of OSA, and it is not a uniform disorder [100]. It is conceivable that those subjects with more frequent and severe hypoxic episodes may benefit to a greater degree than those with milder degrees of respiratory disturbance or hypoxemia. Some studies have suggested that OSA severity may be better defined by examining the percent of time spent per night with oxygen saturations below 90%.

CVD is a leading cause of death in patients with T2DM or OSA. Multiple studies on the effect of CPAP therapy on cardiovascular outcomes in general population and patients with T2DM has been undertaken [101], with some ongoing controversies in the field. CPAP therapy has been shown to improve control of arrhythmias and blood pressure [102]; however, its effect on mortality rate was not established in SAVE RCT, which was attributed to established comorbidities and poor long-term adherence to CPAP therapy [103]. Notably, a recent study confirmed a dose–response relationship between positive airway pressure therapy and major adverse CV events [104]. Further studies are still required to clarify the relative contributions of hypoxemia and sleep fragmentation to disordered glucose control and effect of OSA treatment on complications (hypertension, vascular disease, CKD).

6. Should All Patients with T2DM Be Screened for OSA?

Although obesity, T2DM, and OSA are interrelated, it must be remembered that lean and young patients also can suffer from OSA attributed to cardiovascular autonomic neuropathy [105], and some lean individuals may also exhibit insulin-resistant DM. Metabolic syndrome has been observed in approximately one in three patients with OSA and BMI < 25 kg/m² and approximately two of every three lean non-obese patients with OSA had at least two markers of the metabolic syndrome [106].

One way to separate out effect of DM from obesity with respect to the link to OSA is to study sleep disturbances in those with type 1 DM (T1DM) where obesity is not normally a causal factor, although it may still be present in some individuals with T1DM. A recent review of T1DM and sleep highlights that sleep disorders with subsequent metabolic disturbances occur with increased frequency in normal weight individuals with T1DM [107]. Notably, sleep disturbances in T1DM can result in secondary disturbances in glucose control and neuroendocrine function including elevated night-time levels of growth hormone, epinephrine, and ACTH [108]. Normal weight children with T1DM were shown to have a higher apnoea index when compared to age- and weight-matched non-diabetic children, with the higher apnoea index correlating with poorer glycaemic control [109]. A small study in adults with T1DM found 40% to have OSA [110], and another study similarly showed that daytime sleepiness and OSA was more common in those with T1D than non-diabetic controls, with evidence that cardiovascular autonomic neuropathy was contributing to this [105]. These T1DM studies, while preliminary, clearly support the existence of a link between DM and sleep disorders independent of obesity.

Given that a uniform benefit of treatment of OSA in DM has not been demonstrated, routine screening of the T2DM population with laboratory polysomnography currently cannot be justified in all patients. Ambulatory polysomnography has increasingly replaced laboratory-based polysomnography, and more simplified multiple channel recording devices have been developed to investigate patients with high risk of OSA. Given the high prevalence of sleep disordered breathing in this population, all patients should have an assessment of their potential risk of OSA as part of their routine clinical care. Several questionnaires have been developed for OSA screening. Widely used are the Berlin questionnaire (BQ), STOP-BANG questionnaire (SBQ), Epworth sleepiness scale (ESS), and OSA-50 questionnaire (OSA50) [111–114]. Compared with the BQ, STOP, and ESS, the SBQ is a more accurate tool for detecting mild, moderate, and severe OSA. In subjects with suspected OSA, the SBQ, BQ, and OSA-50 questionnaires, combined with the ESS, can be used to rule in, but not to rule out, clinically relevant OSA [115]. Combined use of the STOP-BANG with different cut-off scores and the ESS facilitates a flexible balance between sensitivity and specificity.

On the basis of current data, treatment of OSA cannot be assured to improve diabetic control although it may be beneficial in some circumstances. These screening tools allow for more effective targeting of investigations and cost-effective treatment in those with T2DM identified with OSA to reduce daytime sleepiness and cardiovascular comorbidities in patients with T2DM.

Much research is needed to better characterise the links between DM, obesity, metabolic dysfunction, and sleep disorders. Many of the existing studies of these relationships are based on relatively small numbers of subjects, raising the possibility of sampling and other biases and confounders. Hence, it would be very useful to try and separate out these variables in large study populations to explore the relationship between discrete factors. For example, studies of sleep patterns in the presence of hyperglycemia or euglycemia in normal weight individuals would assist in determining whether hyperglycemia by itself has a detrimental effect on sleep. Similarly, cardiovascular and sleep studies in normal weight individuals with autonomic neuropathy would remove obesity as a confounder when determining the relationship between autonomic neuropathy, OSA, and cardiovascular disease. Finally, causal relationships would be best established by longitudinal intervention studies where a variable such as glycaemic control or OSA is treated and then the impacts of this treatment measured on the other variables.

7. Conclusions

T2DM and OSA are closely associated and share multiple common mechanisms, including activation of the autonomic nervous system, the inflammatory cascade, and hypoxia-linked endocrinopathy. Evidence is emerging that visceral fat accumulation may be the important element in the development of these conditions. Differences in measurement of fat excess may account for some of the discrepancies in various studies. The role of race and ethnicity is important to maintain consistency as definitions of obesity used in studies of the relationship between OSA and T2DM may differ in different parts of the world. A further challenge is to find a way to control for the effects of variability of CPAP use among patients in different studies. The long-term benefits of CPAP therapy on diabetic control remain questionable. Ultimately, additional studies are needed to better understand the mechanistic cellular and gene pathways underlying OSA and T2DM, which may then allow the intersections between these diseases to be better understood, which might then provide the opportunity to develop novel treatments able to address both conditions at the same time.

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