International Journal of Diabetes in Developing Countries (2021) 41:4–21
https://doi.org/10.1007/s13410-020-00909-1

CONSENSUS

RSSDI clinical practice recommendations for screening, diagnosis, and treatment in type 2 diabetes mellitus with obstructive sleep apnea

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Received: 6 December 2020 / Accepted: 22 December 2020 / Published online: 25 February 2021

Abstract

Purpose of the study Type 2 diabetes mellitus (T2DM) and obstructive sleep apnea (OSA) are closely associated diseases with a significant impact on public health. Both diseases are highly prevalent and the common overlapping risk factors include obesity, old age, and a generally high preponderance in men. A growing body of evidence suggests a bidirectional association between OSA and T2DM; both, in turn, constitute as strong risk factors for cardiovascular diseases, the leading cause of premature deaths and morbidity in India. Several studies have reported a higher prevalence of OSA in Indian patients with T2DM, despite lower levels of obesity. However, OSA remains an underdiagnosed condition in Indian patients with T2DM due to lack of awareness, uncertainty about treatment options, and non-availability of diagnostic facilities.

Methods This document embodies evidence-based clinical practice recommendations and outlines an optimized care pathway for patients with T2DM and OSA, based on consensus multidisciplinary observations and clinical experiences.

Results and conclusions Implementation of screening, diagnosis, and treatment of OSA in patients with T2DM at initial stages could potentially alleviate the risk of cardiovascular disease and substantially improve their quality of life. The recommendations emphasize the need for collaborative efforts from diabetologists, endocrinologists, and sleep medicine specialists towards systematic screening, diagnosis, and treatment of coexisting T2DM and OSA for enhanced patient care.

Keywords Consensus guideline · Continuous positive airway pressure · India · Obstructive sleep apnea · Type 2 diabetes mellitus

Background

The global burden of diabetes mellitus (DM) is rapidly escalating and nearly tripled over the past two decades [1]. According to estimates of the International Diabetes Federation (IDF) 2017,around 463 million or 9.3% of the world's population are living with DM and among these 90% of the cases are type 2 DM (T2DM). India, with over 77 million adults with DM, is ranked second in the world and the estimated number of affected individuals is expected to rise up to 134.2 million by 2045 [1].

Obstructive sleep apnea (OSA) is a common form of sleep-disordered breathing characterized by frequent episodes of partial or complete upper airway blockage resulting in oxygen desaturation and sleep fragmentation and non-refreshing sleep with daytime fatigue and sleepiness [2]. Recent literature-based evidence estimated that approximately 1 billion adults aged 30–69 years worldwide suffer from mild to severe OSA

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and of these 425 million are moderate to severe for which treatment is usually recommended [3]. OSA is also a significant public health problem in India with a prevalence ranging between 3.5% and 19.5%, although a majority of them remain clinically undiagnosed [4].

A growing body of evidence suggests a positive and bidirectional association between OSA and the development of T2DM; both, in turn, constitute as strong risk factors for cardiovascular diseases (CVD), that affect millions worldwide [3, 5–9]. Both diseases share common determinants such as obesity and increasing age and have a higher predisposition in men. Several facets of OSA including short sleep duration and disturbances in the circadian rhythm have recently emerged as potential risk factors for insulin resistance (IR) and development of impaired glucose tolerance and T2DM [10]. Inadequately treated OSA in T2DM is also associated with higher risk of micro- and macrovascular complications including neuropathy, retinopathy, nephropathy, and peripheral arterial diseases. Despite this, OSA remains an underdiagnosed and untreated condition in adults with T2DM due to a general lack of awareness among public and healthcare professionals [11, 12]. The IDF and the American Diabetes Association (ADA) guidelines recommend screening for OSA in all adults with T2DM to reduce diabetes-associated complications [11, 13].

Epidemiology

The prevalence of OSA in adults with T2DM is challenging to define due to the lack of multicenter population-based studies in India. However, several cross-sectional studies across various geographies in India suggest a high prevalence of OSA in adults with T2DM, which varies widely between 23.7% and 95% depending on the study population, methods, and criteria used for diagnosis [14–18]. A hospital-based study from South India on 203 adults with T2DM showed that OSA is prevalent among 23.7% of its study population [14]. A similar prevalence rate for OSA (24.3%) was reported by *Ekka* et al among 325 patients with T2DM in north India [17]. In a study from Central India, among 33patients with T2DM, the prevalence rate for OSA was 27% [15]. A clinic-based cross-sectional study from the Western part of India reported a prevalence rate of 54% among patients with T2DM, which is almost double than other geographies across India [18]. Interestingly, a long-term study by *Malik* et al reported a prevalence rate of over 95% for OSA in north Indian patients with T2DM, which is the highest reported prevalence so far in India [16]. Research studies consistently reported a higher prevalence of OSA in T2DM among men than in women [14, 17, 18]. Moreover, the prevalence of OSA in patients with T2DM among the urban population is higher compared with the rural population [18].

Need for recommendations

The evidence-based Indian initiative on obstructive sleep apnea (INOSA) consensus guidelines stated that the prevalence of OSA in patients with T2DM is higher than those without disease and the risk of developing T2DM increases with the severity of OSA [19]. Existing evidence also suggests that OSA worsens glycemic control in T2DM and may contribute to a higher percentage of diabetes-related complications such as CVD, diabetic neuropathy as well as retinopathy [20].

Given the enormous public health burden, better clinical practices are needed to ensure that patients presenting with either OSA or T2DM are assessed for the co-existence of the other. Both IDF and ADA have already recommended screening for OSA in patients with T2DM [11, 13]. In India, current guidelines for the management of patients with T2DM do not include evaluation for possible OSA. Leading endocrinologists and diabetologists collaborated with sleep specialists to develop this clinical recommendation that provides evidence-based guidance to researchers, patients, clinicians, public health policy-makers, and all other stakeholders' for the screening, diagnosis, and treatment of OSA in patients with T2DM. These recommendations are convened to enable clinical decision making and should be appropriately amended based on the individual patient requirements such as comorbidities, and other factors based on good clinical judgment and practices. These are consensus-based recommendations from the published literature evidence and does not contain any work on animals or human participants conducted by any of the authors.

Obstructive sleep apnea

Signs and symptoms

The pathophysiology of OSA is multifactorial, and the signs and symptoms may vary among the affected individuals. OSA can be mainly grouped under two conditions: present during or around sleep and while the individual is wide-awake [21]. Recurrent collapse of nasopharyngeal and oropharyngeal airways during sleep resulting in substantially reduced (hypopnea) or completely interrupted (apnea) airflow even with constant breathing efforts is a hallmark feature of OSA. Loud snoring is another characteristic manifestation of OSA and in most cases is associated with a brief revival from sleep [22]. An autonomic nervous system stimulation that results in sudden awakening with gasping of air can lead to palpitations, sweating, or even panic [23]. Once the individual is awake, this shortness of breath quickly settles. This sudden awakening can make it difficult to fall asleep again and this is later diagnosed as an OSA. The fragmented sleep, daytime fatigue,

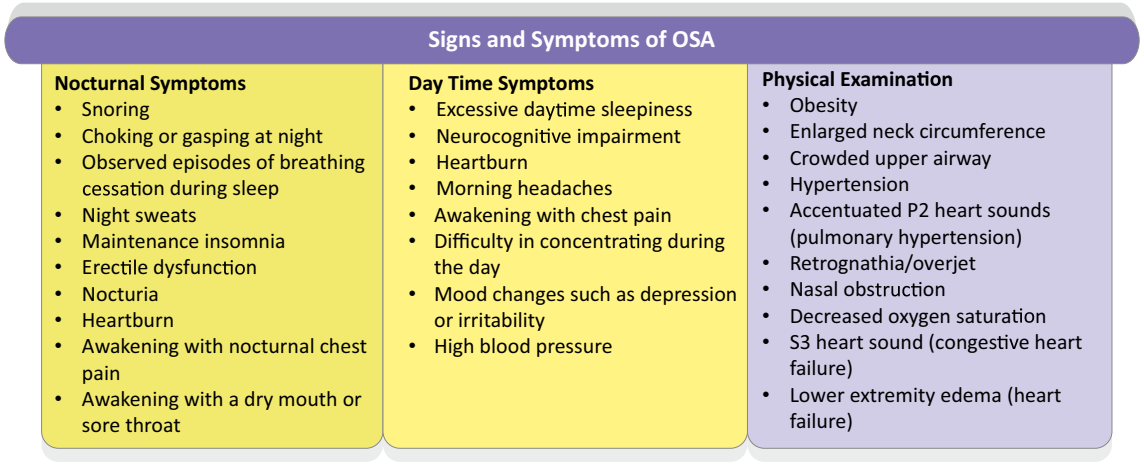

Fig. 1 Signs and symptoms of obstructive sleep apnea. OSA, obstructive sleep apnea; P2, pulmonary valve; S3, third heart sound

and sleepiness are broadly identified as symptoms of OSA [24].

The classical symptoms of OSA mainly involve snoring, excessive daytime sleepiness, choking or gasping at night, night sweats, neurocognitive impairment, heartburn, morning headaches, maintenance insomnia, erectile dysfunction, and nocturia (Fig. 1) [25]. The physical examination findings of OSA mainly comprise obesity, enlarged neck circumference, crowded upper airway, hypertension, accentuated P2 heart sounds (pulmonary hypertension), retrognathia/overjet, nasal obstruction, decreased oxygen saturation, S3 heart sound (congestive heart failure), and lower extremity edema (heart failure) [25].

Screening and diagnosis

Over 80% of individuals with moderate-to-severe OSA remain undiagnosed [26]. Considering the overwhelming impact of OSA on health and quality of life, it is important to effectively diagnose patients with OSA and ensure optimal management [27–30]. Thus, an appropriate screening tool is essential to categorize patients based on their clinical symptoms and physiological risk factors.

The prospective diagnostic strategy mainly includes an assessment of a formal clinical history using screening questionnaires, clinical questionnaire tools, and prediction tools [23]. Screening questionnaires are simple, low-cost tools that can be used to segregate patients eligible for diagnostic tests. The US Preventive Services Task Force recommends the Epworth Sleepiness Scale (ESS) [30], STOP Questionnaire (Snoring, Tiredness, Observed Apnea, High Blood Pressure) [31], STOP-Bang Questionnaire (STOP Questionnaire plus body mass index [BMI], Age, Neck Circumference, and Gender) [32], the Berlin questionnaire [33], and the Wisconsin Sleep Questionnaire [34] to screen patients with OSA in primary care setting [35] (Fig. 2).

In addition to the risk factors, physical examination comprising BMI, reduced distance and increased angles from the chin to the thyroid cartilage, and a narrow oropharyngeal opening can be predictive of OSA [24, 25]. Individuals screened positive would have to undergo a diagnostic test to confirm the presence of OSA. Polysomnography (PSG) is a noninvasive, sleep laboratory, or home-based testing using a portable monitor to quantify apnea-hypopnea index (AHI), calculated by adding all number apnea and hypopnea events and then dividing it by total sleep time. PSG involves simultaneous recording of OSA determinant physiologic sleep variables such as electroencephalogram, electrooculogram (eye movements), chin electromyogram (muscle tone), electrocardiogram, respiratory effort, airflow, and oxygenation [36].

OSA-excess weight-T2DM

Several longitudinal cohort studies and meta-analysis have reported an increased risk of poor metabolic control and incident T2DM in patients with severe to moderate sleep apnea [37–40]. Findings also suggest that self-reported history of sleep-disordered breathing and snoring are independently associated with glucose intolerance and insulin resistance in patients with T2DM [27, 41, 42]. Aggregated with aging and obesity, OSA has shown to increase the risk and severity of T2DM [43, 44]. Interestingly, Indian patients with T2DM with a low BMI are also at risk of developing OSA. In an Indian study with over 400 T2DM patients from a specialty diabetes clinic, nearly 28% of patients with BMI ≤ 25 kg/m^2 had a high risk of OSA as assessed on the Epworth Sleepiness Scale [45]. Thus, epidemiologically Indians and South Asians have a similar risk of OSA as compared with Americans or Europeans despite lower rates of obesity [46].

Obesity is a predominant risk factor and a 10% increase in body weight has been correlated with a six-fold increase in the risk of developing OSA [47]. Sleep fragmentation due to

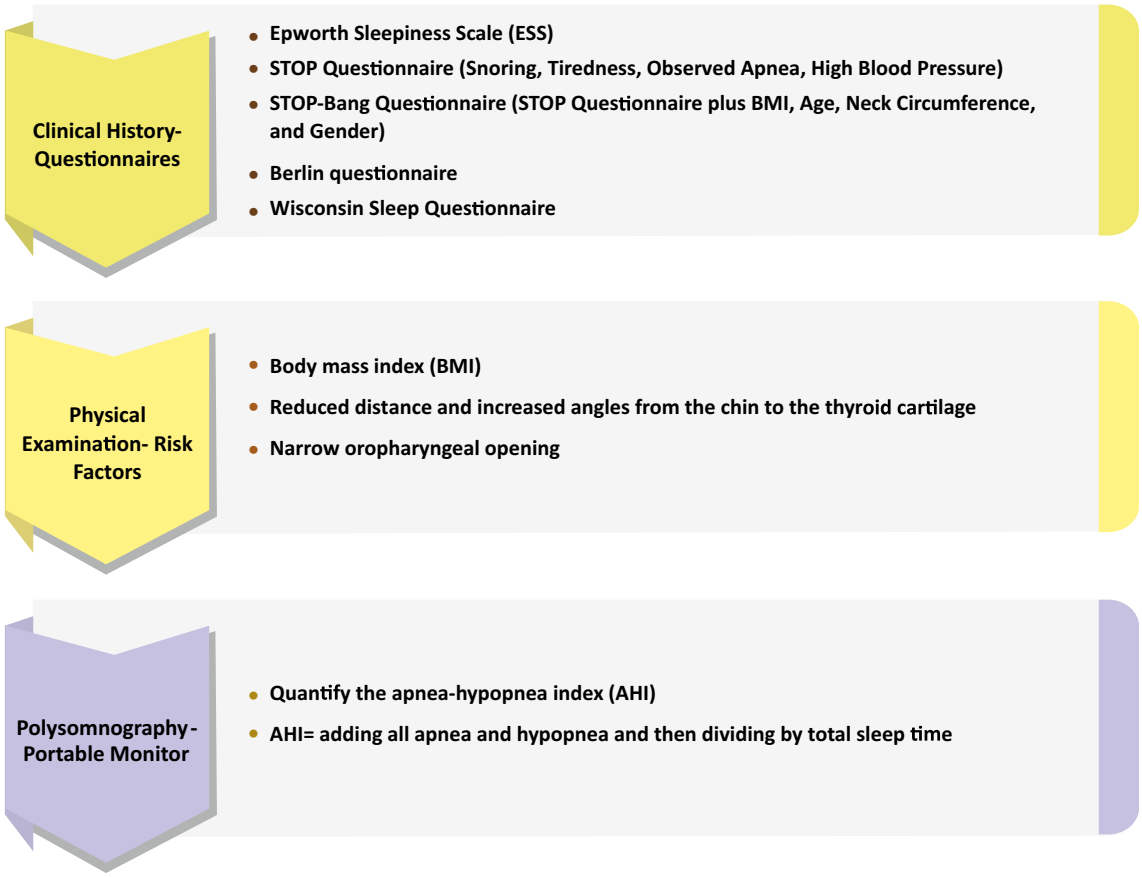

Fig. 2 Diagnosis of obstructive sleep apnea

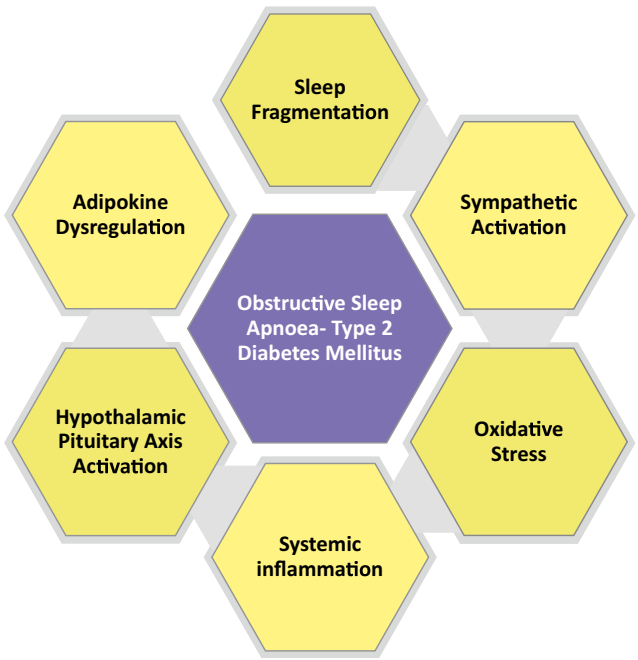

Fig. 3 Plausible mechanisms of development of glucose intolerance in OSA-T2DM patients

sudden awakening during sleep leads to activation of the autonomic nervous system. Augmented oxidative stress and chronic inflammation due to intermittent hypoxia and enhanced sympathetic activity dysregulate the glucose metabolism. It is further postulated that hypoxia may have damaging effect on pancreatic β-cell, liver, and adipose tissue function, which could further disrupt the glucose homeostasis [48] (Fig. 3).

Insufficient (≤ 5 h/day) or excessive (≥ 9 h/day) sleep interval is associated with a risk of developing T2DM, which is comparable with physical immobility or inactivity. The mechanism of glycemic dysregulation and obesity with sleep disturbances is mainly linked with overactivity of the sympathetic nervous system that triggers over-eating or binge eating and commonly reported in patients with T2DM; this is ultimately linked to excessive weight gain [43]. Dysregulation of neuroendocrine control of appetite associated with disturbed sleep leads to increased circulating levels of hunger promoting hormone (ghrelin) and decreased satiety factor (leptin) [49]. Prevalence of undiagnosed OSA (86.6%) is currently high in obese patients with T2DM [50].

Earlier studies comparing insulin resistance in total sleep-deprived individuals versus those with normal sleep conditions demonstrated that insulin resistance was induced by

acute sleep deprivation [51, 52]. Findings from a randomized controlled study suggested that an improvement of sleep pattern in obese patients with T2DM significantly reduced body weight, BMI, and glycated hemoglobin (HbA1c) as compared with the control group [53]. Confirming the two-way link, the Sleep AHEAD randomized controlled study reported clinically relevant improvements in OSA among obese patients with T2DM following lifestyle-based behavioral weight loss program and increased physical activity [54]. The benefit of weight loss was observed in men with severe OSA at baseline and participants with a weight loss of 10 kg or more who showed the greatest reductions in AHI [48]. Thus, effective weight loss strategies could produce meaningful improvements in outcomes among patients with OSA and T2DM.

Current treatment options for OSA

There are several options available for the management of OSA according to disease severity, which include:

- Lifestyle modifications such as weight loss through physical exercise for all obese people with OSA should be recommended for regardless of other interventions. Additionally, risk factors such as alcohol, smoking, and sedative medications should be avoided.
- Continuous positive airway pressure (CPAP) is regarded as the gold standard treatment for OSA. Patients with AHI ≥ 5 with symptoms or AHI ≥ 15 are primarily recommended for treatment with auto-CPAP therapy, as a first line of therapy [55]. During CPAP treatment, the pressurized air is delivered into the upper airways, to relieve obstruction during sleep [56, 57]. The mask is worn over the nose and/or mouth while sleeping, which is connected to the machine that delivers pressurized air continuously [58]. Despite all benefits, patient's intolerance, unacceptance, and non-adherence due to mask discomfort may limit the use of CPAP. Therefore, counseling, and open discussion with patients should be encouraged to mitigate apprehensions and negative perceptions about CPAP. Bi-level positive airway pressure (PAP) may be considered in patients who are intolerant to CPAP and is suitable for non-obstructive sleep-related hypoventilation and patients with overlap syndromes leading to hypoventilation. It works by administering pressure between inspiratory and expiratory cycles thereby combating the inspiratory flow limitation of the upper airway and increasing the tidal volume. This noninvasive method is considered more appropriate for obese patients with hypoventilation, patients with chronic obstructive pulmonary disorder, or alveolar hypoventilation associated with neuromuscular disorders [59].
- Oral appliances are widely prescribed as a treatment for OSA in patients with mild-to-moderate OSA, particularly in patients who are unable to use CPAP [60]. These are known to alleviate airway obstruction by enlarging the upper airway or reducing its collapsibility during sleep [61]. A dental device can be used to keep the airway open, which is noninvasive in nature and has emerged as an alternative treatment for OSA. Oral devices are categorized as tongue-retaining devices and mandibular advancement devices (MAD) or mandibular advancement splints (MAS) or mandibular repositioning appliances (MRA) [62, 63]. The MAD is more widely applied in clinical practice. MAD appliances enable mandibular protrusion with respect to the resting position by covering the upper and lower teeth, which in turn advances the tongue position and subsequently increases oropharyngeal volume. Accredited sleep specialists may predict an effective mandibular protrusion position by using polysomnographic evaluation with a remotely controlled mandibular positioner to help customize the device [64]. In patients with mild-to-moderate OSA, a > 50% reduction in AHI to < 5/h was reported in 42.8% of patients using an oral appliance and 73.2% of patients using CPAP. The odds of achieving AHI < 5/h was 49 times greater and < 10/h 89 times greater in patients treated with the oral appliance when compared with the control untreated group [65, 66]. The tongue-retaining devices hold the tongue forward by suction, thereby avoiding its collapse into airways. However, these devices have poor tolerance among patients and have shown inadequate efficacy [60, 66]. Objective tracking of device use and adherence is usually challenging. However, the difference between the mean subjective adherence rates for oral appliance users was 0.70 more hours per night than the objective adherence rates among CPAP users [65, 66].
- Surgery is warranted in few conditions that need anatomical restructuring to reduce the obstruction in nose, oropharynx, or hypopharynx. Such conditions include retro positioned maxilla or mandible, enlarged pharyngeal fat pads, soft palate or tongue, narrow posterior airway space, and upper airway hypotonia. Nasal surgeries, palatal surgeries (uvulopalatopharyngoplasty), and tongue-based surgeries (genioglossus advancement with hyoid suspension) are performed at level 1 to alleviate OSA maxillomandibular advancement (MMA) is a more complex procedure and generally reserved for patients with major OSA and for obstructions that could not be resolved in level 1 surgeries [63, 67].

Biological links/pathophysiology between OSA and T2DM

Obesity is a major confounder for the association between T2DM and OSA [68]. Nearly 60–90% of individuals with

OSA are overweight, and the relative risk of OSA in obesity (BMI > 29 kg/m^2) is ≥ 10 [11]. Several studies report a substantial impact of fat accumulation around the abdomen and neck regions on upper airway size and function. Increasing neck circumference, reduced pharyngeal lumen size, and compromised upper airway muscle force due to fat deposition in obese individuals leads to occlusion of the upper airway during sleep, resulting in OSA [69]. Additionally, reduced lung volume and upper airway size secondary to increasing mass effect of central obesity on the chest wall and reduced tracheal traction worsens hypoxia and contributes to increased risk of OSA [70]. The relationship between OSA and T2DM is bidirectional: OSA is a risk factor for T2DM and vice versa [9]. The following sections outline the postulated links.

Does OSA play any role in the development of T2DM?

OSA may directly or indirectly play a role in development of T2DM. The intermittent hypoxia and sleep fragmentation are postulated to induce metabolic dysfunction and alteration of glucose metabolism that eventually contributes to the development of T2DM [71] (Fig. 4). Episodes of hypoxia also reduce insulin sensitivity without a compensatory increase in insulin secretion, potentially suggesting β-cell dysfunction. Other mechanisms associated with disrupted glucose metabolism include hormonal changes such as activation of the hypothalamic–pituitary–adrenal axis; higher release of catecholamines, ghrelin, leptin; and decreased adiponectin in OSA. Further, recurrent hypoxia and sleep arousals contribute to increased sympathetic activity leading to dysregulation of glucose and fat metabolism and the development of T2DM. Oxidative stress in OSA and the elevated levels of inflammatory cytokines such as tumor necrosis factor alpha, interleukin-6 (IL-6), IL-8, and nuclear factor kappa light chain enhancer of activated B cells NF-κB also contribute to IR and β-cell dysfunction [72].

Does OSA have any effect on components of metabolic syndrome?

Metabolic syndrome is a group term for several metabolic abnormalities including central obesity, IR or glucose intolerance, hypertension, and dyslipidemia, and is associated with an increased risk for T2DM and CVDs [73]. Several studies identified an independent and bidirectional risk association between OSA and metabolic syndrome or its individual components [74, 75]. Moreover, the severity of OSA is associated with poor control of components of metabolic syndrome such as hyperglycemia, hypertension and dyslipidemia [76, 77]. Existing literature evidence suggests that OSA initiates several intermediary mechanisms such as inflammation, neurohumoral alterations including sympathetic activation, and oxidative stress that have been suggested to increase the risk of metabolic syndrome as well as its components [78].

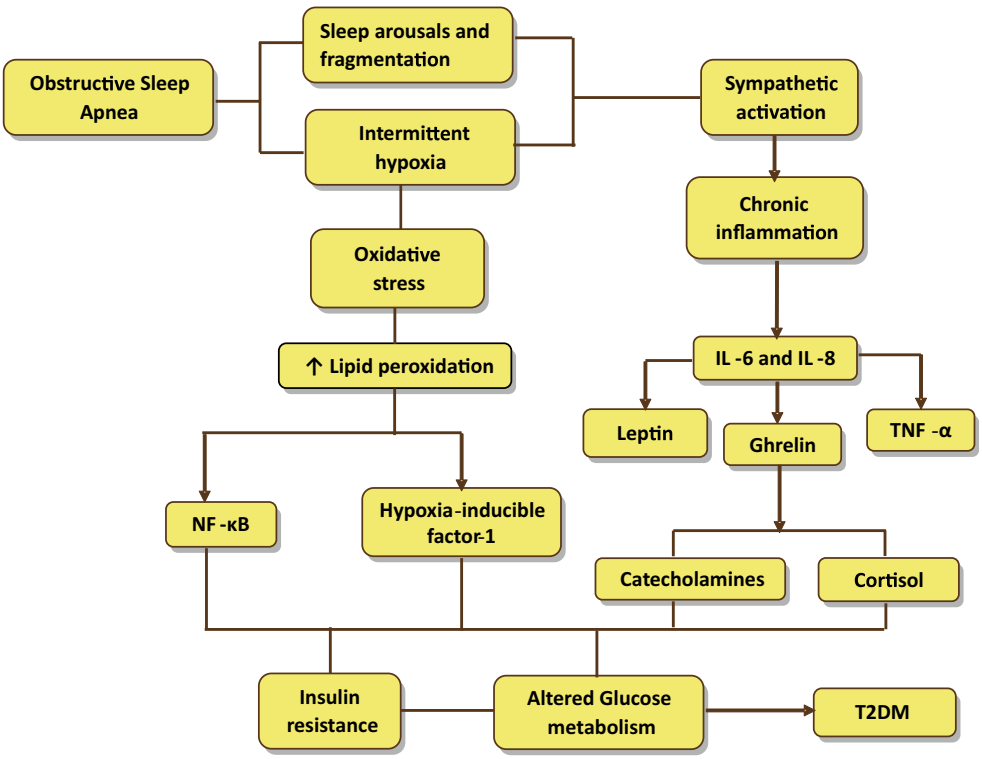

Fig. 4 Link between OSA and T2DM. OSA, obstructive sleep apnea; IL, interleukin; NF-κB, nuclear factor kappa light chain enhancer of activated B cells; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor alpha

Does T2DM play a role in the development of OSA?

The role of T2DM as a risk factor for OSA is less explored. In a study evaluating risk factors (odds ratio [95% CI]) for OSA in a population of 3565 individuals, waist circumference (1.34 [1.19–1.52]), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR) (1.31 [1.13–1.51] both) and triglycerides (1.24 [1.09–1.41]) were associated with a greater risk of observed apnea [79]. Notably, these risk factors are commonly associated with T2DM. It is postulated that T2DM can contribute to the development or exacerbated progression of pre-existing OSA. Increasing body weight in T2DM is the most common determinant of OSA that has a higher preponderance in men [80]. Among other possible mechanisms, loss of upper airway innervation and reduced neuromuscular response due to autonomic neuropathy in diabetes explains the abnormal control of breathing and frequent sleep apnea in these patients [80–82].

Does OSA have any effect on glycemic control of existing T2DM patients?

Several cross-sectional studies have suggested that OSA has a significant impact on the glucose metabolism and glycemic control in both patients with or without T2DM [83, 84]; however, data from long-term prospective longitudinal studies are lacking. Existing literature shows that both presence and severity of untreated OSA independently associate with poor glycemic control (increased HbA1c levels) in patients with T2DM; despite adjusting for relevant confounding factors such as age, sex, race, BMI, diabetes duration, lipids, exercise, blood pressure and insulin therapy [83, 85, 86]. Moreover, both duration and quality of sleep were also correlated with worse glycemic control; necessitating the need for treatment of OSA in patients with T2DM [87]. However, the effect of CPAP therapy on glycemic control or IR have had mixed results in patients with T2DM (Table 1).

Public health implications of OSA and T2DM

Both OSA and T2DM are closely associated diseases with high prevalence and having major impact on public health. There is increasing evidence that OSA is associated with risk of both T2DM and CVD complications; resulting in significant socioeconomic burden [1, 11, 13, 88]. It is likely that over half of the people with T2DM suffer from sleep disturbances and of these, up to one-third who are severely affected may require treatment [11].

Literature evidence shows that the presence and severity of OSA in patients with T2DM have been implicated in macro- and microvascular complications of diabetes mellitus [88]. OSA shares several common molecular mechanisms with hyperglycemia which results in microvascular complications in patients with T2DM [88]. In patients with T2DM, the presence of OSA was associated with the risk of diabetic retinopathy [89], diabetic macular edema [90], diabetic neuropathy [91], and diabetic nephropathy [92]. It was also well-established that OSA in patients with or without T2DM was strongly implicated for CVD in numerous cross-sectional and longitudinal studies [93, 94]. In both Sleep Heart Health Study and the Wisconsin Sleep Cohort Study, OSA was strongly associated with hypertension [7, 95, 96]. Moreover, OSA is the most common secondary cause of drug-resistant hypertension and linked to a non-dipping form of hypertension [7, 97]. Though studies in patients with T2DM are lacking, OSA has been associated with a higher risk of developing coronary artery disease [5], stroke [98], atrial fibrillation [99], atherosclerosis [100], dyslipidemia [101], arterial stiffness [102], cardiac arrhythmias [103], and heart failure [5]. Other comorbidities that have been associated with OSA include cognitive impairment, depression, decreased quality of life, motor vehicle accidents, psychological social function, and erectile dysfunction [88].

The high prevalence of OSA in T2DM raises the likelihood that some of the morbidity and mortalities linked to T2DM may be attributable to undiagnosed OSA [50]. This was clearly evident in the Sleep AHEAD trial where alarmingly 86% of obese patients with T2DM were found to have undiagnosed OSA with an AHI of 20.5 events/h [50]. In a 10-year long-term observation study, obese patients with OSA had higher healthcare resource utilization and associated costs; interestingly these were increased over time until diagnosis and decreased after treatment [104]. Therefore, even in the absence of clinical manifestations, physicians handling obese patients with T2DM should be screened and treated appropriately as a part of routine clinical practice for better health outcomes associated with adverse consequences of OSA [50, 105].

Recommendations for screening of patients for OSA for diabetologists [19, 106–108]

Figure 5 outlines the recommendations for screening, diagnosis, and treatment of OSA in patients with T2DM. As discussed, any of the validated, easy-to-use questionnaires (STOP, STOP-Bang, Berlin Questionnaire, Epworth Sleepiness Scale, or Wisconsin Sleep Questionnaire) can be used for screening. STOP and STOP-Bang are reliable tools with high sensitivity to detect mild, moderate, and severe OSA in clinical settings [109]. Patients presenting with the following signs and symptoms are considered as high risk and should be screened for OSA:

Table 1 Studies on the effects of CPAP on glucose metabolism in prediabetes and T2DM

Studies	Year	Number of study population	Study design	OSA definition	Baseline characteristics	Duration	Adherence (hours/night)	Glucose parameters measured	Findings
Prediabetes									
Weinstock et al. [110]	2012	50 adults (CPAP/sham: 25 and sham/CPAP: 25) with IGT (2-h OGTT ≥140 mg/dL)	Crossover	AHI ≥15		8-weeks	CPAP: 4.8 Sham: 3.4	Fasting and 2-h glucose, fasting, and 2-h insulin, insulin sensitivity (Gutt index), HOMA	No difference in glucose parameters. No reversal of IGT. Insulin sensitivity and 2-h insulin level improved only in severe OSA (AHI ≥30)
Pamidi et al. [111]	2015	39 (CPAP: 26 and placebo: 13) with prediabetes (FPG 100–125 or 2-h glucose 140–199 mg/dL, or both)	Parallel group	AHI ≥5		2 weeks	CPAP: 8	Fasting and 2-h glucose and insulin, insulin, AUC glucose, and insulin (OGTT); insulin sensitivity (IVGTT)	Improvement in insulin sensitivity and AUC glucose but no differences in other parameters
T2DM									
West et al. [112]	2007	42 (CPAP: 20 and control: 22)	Parallel group	ODI ≥10	CPAP: HbA1c 8.5%. Sham: HbA1c 8.4%	3 months	CPAP: 3.3 Sham: 3.5	HbA1c, insulin sensitivity by HOMA, and euglycemic hyperinsulinemia clamp	No difference in glucose parameters but improved sleepiness
Myhill et al. [113]	2012	44 early (i.e., 1 week) or late (i.e., 1 to 2 months) CPAP start	Parallel group	AHI ≥15	CPAP: HbA1c 6.9% (9.3% diet controlled, 62.8% OHA, 27.9% insulin and OHA)	3 months	CPAP: 5.4	HbA1c	No difference in glucose parameters. Significant reduction in SBP and DBP (9 and 7 mmHg, respectively)
Shaw et al. [114]	2016	256 (CPAP: 119 and usual care: 137)	Parallel group	ODI ≥15	CPAP: HbA1c 7.3% (47% diet controlled, 53% medications). Usual care: HbA1c 7.3% (54% diet controlled, 46% medications)	6 months	CPAP: 4.3 (at 3 months) and 4.9 (at 6 months)	HbA1c, fasting glucose	No difference; decreased DBP in adherent group, improved QOL, and decreased sleepiness
Martinez-Ceron et al. [115]	2016	50 (CPAP: 26 and untreated: 24)	Parallel group	AHI ≥5	CPAP: HbA1c, 7.6%. No treatment: HbA1c, 7.6% (58% OHA, 36% insulin, 6% OHA and insulin)	6 months	CPAP: 5.2	HbA1c, fasting glucose and insulin, insulin sensitivity (HOMA and QUICKI)	Decreased HbA1c levels, mean difference, 0.4% Decreased fasting insulin levels Improved insulin sensitivity decreased IL-1b, IL-6, and adiponectin
Mokhlesi et al. [116]	2016	19 (CPAP:13 and sham: 6)	Parallelgroup	AHI ≥5	CPAP: HbA1c, 7.3% (46% diet controlled, 54% OHA) Sham: HbA1c, 7.0% (33% diet controlled, 66% OHA)	1 week	CPAP: 7.9 Sham: 7.9	Plasma glucose measured by 24-h blood sampling	Decreased plasma glucose, predominantly at night and morning fasting, reduced serum insulin (nonsignificant trend)

Table 1 (continued)

Studies	Year	Number of study population	Study design	OSA definition	Baseline characteristics	Duration	Adherence (hours/night)	Glucose parameters measured	Findings
Morariu et al. [117]	2017	23 (CPAP:12 and sham: 11)	Parallel group	Previously untreated OSA	CPAP: HbA1c 6.6%Sham: HbA1c 6.9% (OHA only)	1 month	CPAP: 4.1 Sham: 4.5	Fructosamine, 24-h interstitial glucose profile by continuous glucose monitoring for 3 days	Significant reduction in fructosamine No difference in 24-h glucose profile
Lam et al. [118]	2017	64 (CPAP: 32 and untreated: 32)	Parallel group	AHI ≥15	CPAP: HbA1c 8.1% (78% OHA, 22% OHA and insulin). No treatment: HbA1c 8.4% (62% OHA, 38% OHA and insulin)	3 months	CPAP: 2.5	HbA1c, fasting glucose	No difference in glucose parameters but after excluding dropouts and those with medication changes, CPAP resulted in a reduction in HbA1c of 0.4%. Significant reduction in SBP and DBP (10 and 6 mmHg, respectively)

AHI, apnea-hypopnea index; *AUC*, area under the curve; *CPAP*, continuous positive airway pressure; *DBP*, diastolic blood pressure; *FPG*, fasting plasma glucose; *HbA1c*, hemoglobin A1c; *HOMA*, homeostatic model assessment; *IGT*, impaired glucose tolerance; *IL*, interleukin; *IVGTT*, IV glucose tolerance test; *ODI*, oxygen desaturation index; *OGTT*, oral glucose tolerance test; *OHA*, oral hypoglycemic agent; *OSA*, obstructive sleep apnea; *QOL*, quality of life; *QUICKI*, quantitative insulin sensitivity check index; *SBP*, systolic blood pressure; *T2DM*, type 2 diabetes mellitus

- Patients complaining of sleepiness, non-restorative sleep, fatigue or symptoms of insomnia, waking up with gasping or choking, habitual snoring, interruptions in breathing
- Upper airway evaluation showing retrognathia, high arched palate, macroglossia, tonsillar hypertrophy, enlarged uvula, and nasal abnormality
- Patients who demonstrate PSG or level 3 portable sleep test or home-based cardiorespiratory sleep tests with five or more obstructive respiratory events per hour of sleep OR with fifteen or more obstructive respiratory events per hour of sleep in the absence of symptoms
- Existing comorbidities such as hypertension, prediabetes or overt T2DM, congestive heart failure, atrial fibrillation, coronary artery disease, and cognitive dysfunction
- Patients with BMI > 22–25 kg/m^2 [119]
- Abdominal obesity (cm) in the range of > 90 for males and > 80 for females (Asian population) and waist circumference men: 78 cm, women: 72 cm
- Neck circumference—women: > 16 in.; men: > 17 in.
- Body fat cut—men: 25%, women: 30%
- Fasting plasma glucose (FPG) ≥ 100 mg/dL
- Hypertension (mmHg) ranging in ≥ 130/≥ 85
- High triglycerides levels of ≥ 150 and low levels of high-density lipoprotein (HDL)men: < 40; women: < 50

Additionally, patients with congestive heart failure, atrial fibrillation, treatment-refractory hypertension, nocturnal dysrhythmias, hypothyroidism, stroke, and pulmonary hypertension are also at increased risk of OSA and should be screened for the same [108]. Notably, candidates for bariatric surgery and individuals on high-risk jobs (machine operators, pilots, truck or bus drivers) experiencing excessive daytime somnolence should be screened for possible OSA.

Recommendations for diagnosis

Diagnosis of T2DM in patients with OSA

Diagnosis of prediabetes and T2DM is recommended in family members of patients with existing T2DM and overweight children and adolescents at the onset of puberty. Overweight individuals exhibiting signs and symptoms of OSA especially habitual snoring, witnessed apnea, and daytime sleepiness should be diagnosed for the co-existence of T2DM.

Prediabetes can be diagnosed based on the following criteria [120]:

- Impaired fasting glucose (IFG): FPG 100 mg/dL to 125 mg/dL or

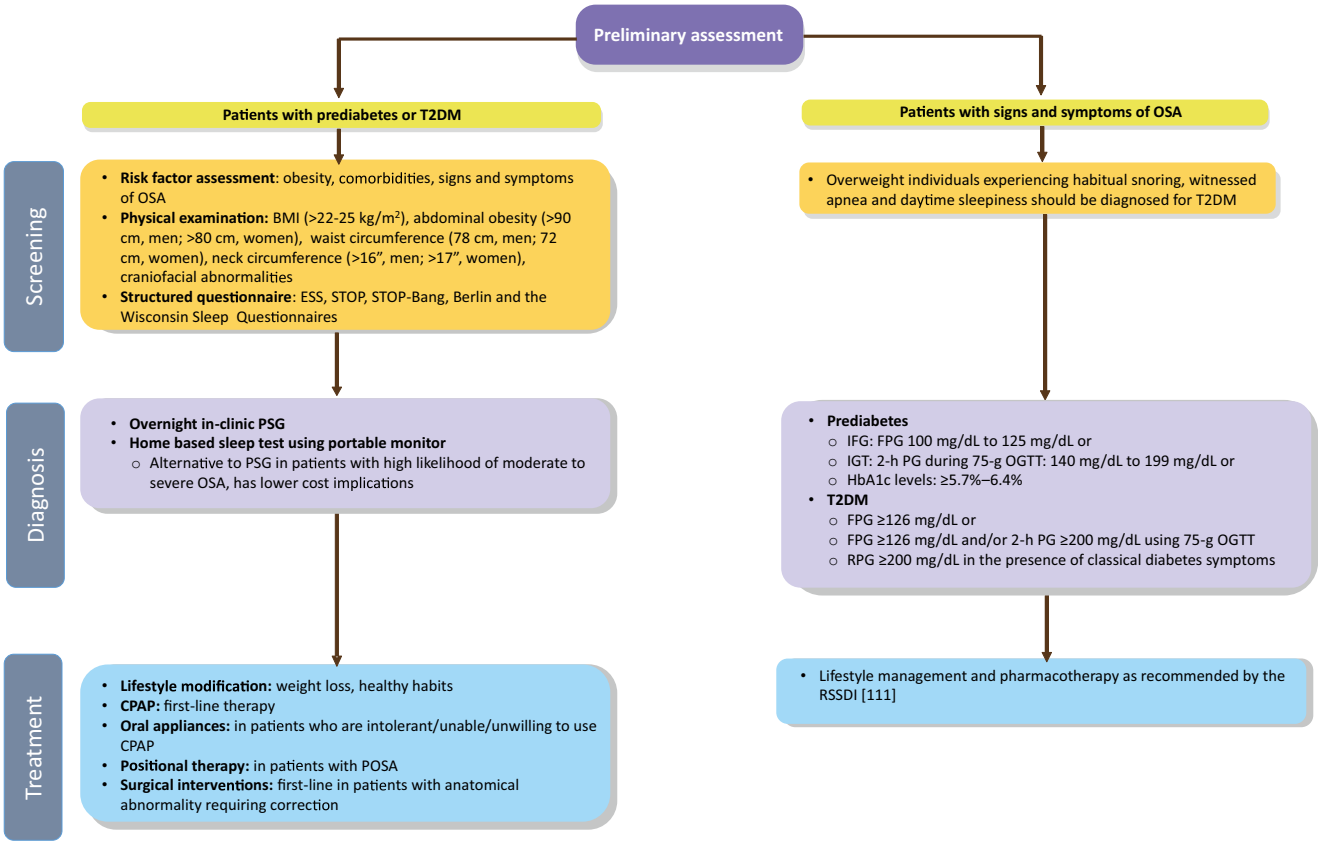

Fig. 5 Recommendations for screening, diagnosis, and treatment of OSA in patients with T2DM. AHI, apnea-hypopnea index; BMI, body mass index; CPAP, Continuous positive airway pressure; ESS, Epworth Sleepiness Scale; FPG, fasting plasma glucose; IFG, Impaired fasting glucose IGT, Impaired glucose tolerance OGTT, oral glucose tolerance test OSA, obstructive sleep apnea; POSA, Positional obstructive sleep apnea; PSG, polysomnography RPG, random plasma glucose; RSSDI, Research Society for Study of Diabetes in India; T2DM, type-2 diabetes mellitus

- Impaired glucose tolerance (IGT): 2-h plasma glucose (2-h PG) during 75-g, oral glucose tolerance test (OGTT) 140 mg/dL to 199 mg/dL or
- HbA1c levels ranging from ≥ 5.7%–6.4%

The diagnosis of T2DM should follow the following criteria [120]:

- FPG ≥ 126 mg/dL or
- FPG ≥ 126 mg/dL and/or 2-h PG ≥ 200 mg/dL using 75-g OGTT
- Random plasma glucose ≥ 200 mg/dL in the presence of classical diabetes symptoms

Diagnosis of OSA in patients with T2DM

Eligible patients (determined using questionnaire-based prediction algorithm) should be subjected to overnight monitoring using PSG by trained personnel [109, 121]. The diagnosis of OSA is to be confirmed if one of the two conditions exist [122]:

≥15 events of apnea, hypopnea, or increased respiratory effort leading to sleep arousals per hour of sleep in asymptomatic patient, with >75% of apnea/hypopnea events being obstructive	≥5 events of apnea, hypopnea, or increased respiratory effort leading to sleep arousals per hour of sleep in patients with signs and symptoms of disturbed sleep, with >75% of apnea/hypopnea events being obstructive

The AHI cut-offs for diagnosis of OSA measured on the PSG are as follows [26]:

- Mild OSA: 5 to 15 episodes/h
- Moderate OSA: 15–30 episodes/h
- Severe OSA: ≥ 30 episodes/h

Do not exclude the diagnosis of OSA based on a negative or indecisive polysomnogram. It is highly recommended to

repeat PSG especially in high-risk patients with predisposing variables [123].

As PSG is an expensive, time-consuming test requiring trained technicians, portable monitoring may be used as an alternative to diagnose OSA only in patients screened as highly probable to manifest moderate to severe OSA [124]. Testing of sleep-disordered breathing using level 3 portable devices may expedite diagnosis and considerably lower the costs associated with level 1 in-clinic PSG [19]. Level 3 portable devices have demonstrated adequate diagnostic performance compared with level 1 sleep tests in adult patients with moderate to severe OSA and having a high pretest probability with no unstable comorbidities [125]. Home-based cardiorespiratory sleep tests or cardiopulmonary may also be an acceptable approach for initial screening of patients with a suspicion of OSA, especially children or morbidly obese individuals [126, 127]. If the portable or home-based test is negative or inclusive, PSG should be performed for confirmatory diagnosis. Portable or home-based testing is discouraged in patients with comorbid neuromuscular diseases, moderate to severe pulmonary diseases, congestive heart failure, movement disorders, severe insomnia, history of stroke, sleep seizures, etc. [109, 121].

Patients diagnosed with OSA and recommended CPAP should be brought back to the sleep clinic for follow-up PSG to enable titration of CPAP pressure. If clinically suitable, a split-night protocol may be followed: part 1-diagnosis of OSA with at least 2 h of recorded sleep; part 2—titration of CPAP. This is recommended in high-risk patients with ≥20 events/h or ≥40 events/h in low-risk patients in part 1. The split-night protocol is a cost-effective approach that facilitates timely delivery of treatment [109].

Recommendations for treatment of OSA in prediabetes and T2DM

The treatment options for OSA in patients with T2DM who are at CVD risk include lifestyle modification, pharmacotherapy, and medical management, which include devices such as positioning therapy, CPAP therapy or dental appliances, and surgical interventions [128].

Lifestyle modification

- **Weight loss:** Weight loss achieved from either dietary or surgical procedures are shown to be associated with improvement in OSA severity [129, 130].

– Weight loss is considered as the primary treatment strategy for OSA in individuals who are overweight or obese and therefore, should be recommended in addition to other therapies

Exercise and a healthy diet should be adopted for weight control.
Bariatric surgery is another major option for patients in which weight loss through diet and exercise has failed.

- **Healthy habits:** [128]

– Alcohol and smoking cessation should be promoted to minimize further risk.
– Avoid medications that could aggravate sleep apnea, such as central nervous system depressants (i.e., opiates and benzodiazepines).

Pharmacotherapy

Role of pharmacotherapy in the management of OSA is limited [131].

- Currently, there are no widely effective pharmacotherapies to recommend for patients with OSA. However, treatment of chronic or seasonal nasal congestion could be improved with an appropriate regimen of antihistamines, decongestants, nasal steroids, and/or saline irrigation.

Medical management

Positional therapy

In this therapy, patients are maintained in a non-supine position during sleep using a positioning device, as it is associated with a higher reduction in upper airway dimension. It was found that over half of all patients with an AHI >5 events/h have a positional component to their OSA [132].

- Positional therapy can be used as a supplemental to primary therapy.

Continuous positive airway pressure

There are conflicting results on the effect of CPAP on the glucose metabolism in people with prediabetes and T2DM (Table 1**),** owing to small sample size and lack of control subjects. However, CPAP is considered as a gold standard and first line of therapy due to its favorable effects on sleep quality and quantity and subsequent prevention of T2DM and CVDs. Literature

evidence shows that patients with OSA who are highly adherent to CPAP therapy may have a greater likelihood of deriving metabolic benefit and lower risk of all-cause mortality due to CVDs [133, 134]. Moreover, the CPAP treatment has beneficial effects on quality of sleep that improves the fatigue and daytime sleepiness and consequently reduces vehicle accidents and work impairment [135].

- CPAP should be considered as a first-line of therapy.

Oral appliances

Oral appliances, such as tongue-retaining and mandibular advancement devices, works by mechanically enlarging the upper airway tract; however, these are less efficacious than CPAP therapy [66, 136].

- Oral appliances are recommended for the treatment of OSA in patients who are intolerant to or unable or unwilling to use CPAP therapy.

Surgical interventions

Surgery is performed to unblock the obstruction in the upper airway using different surgical procedures depending on the anatomic level at which obstruction occurs (nasal, upper pharyngeal, lower pharyngeal, or global upper airway) [128]. Inherent to any other surgical procedures these are limited by pre and post-operative complications [128].

- Surgery should be considered as a second-line of therapy for patients with OSA who are intolerant or experience a poor response to or CPAP therapy. However, it is considered as a first-line of therapy in pediatric patients and in those with significant anatomical abnormality requiring correction [137].

Recommendations of patient care

There is an evident need for healthcare professionals to be conscious, educated, and well-trained in the area of OSA and T2DM.

These clinical recommendations endorse IDF consensus guidelines on OSA in patients with T2DM and recommend the following:

- Healthcare professionals working on both T2DM and OSA should adopt adequate clinical practices to ensure that individual presenting with one clinical condition is considered for treatment of the other.
- Healthcare professionals should aim to develop routine interventions that are appropriate for both T2DM and OSA.

Sleep services

- Individuals with OSA must be routinely screened for markers of metabolic abnormalities and cardiovascular risk factors

  – At least waist circumference, blood pressure, fasting lipids, fasting glucose should be included as a part of the screening process.

Diabetes services

- The possibility of OSA should be considered in the assessment of all individuals with T2DM and metabolic syndrome.

  – All individuals with T2DM should be assessed for symptoms of OSA: snoring, apnea during sleep, and daytime sleepiness.

- Individuals with T2DM should be referred to a specialist at an early stage so as to diagnose and subsequent therapy owing to confirmed benefits on hypertension and quality of life.

  – Management of OSA should focus primarily on weight reduction in overweight and obese people.
  – CPAP is the current best treatment for moderate to severe OSA and should be considered where appropriate.
  – Recommend cessation of smoking and alcohol intake.
  – Recommend oral appliances or surgery where appropriate.

Recommendations for promotion of research

Further research is warranted, owing to the direct impact of OSA in T2DM on the individual's life and its economic burden on both individuals as well as society, in the following areas:

- **Epidemiological studies**

  – All data in patients with T2DM are limited with cross-sectional studies; hence, long-term nationwide

prevalence studies of OSA in adults with T2DM are warranted.

Studies in children with obesity, different ethnic groups, and adults with gestational diabetes and pre-eclampsia are of more interest.

- **Mechanistic studies**
  It is recommended that all healthcare professionals who are involved in T2DM or OSA must be educated about the links between the two conditions and trained appropriately for patient care.

– Further studies are required to better understand the biological links between OSA and T2DM, and to improve treatment and patient care, in the following areas.

  - Effect of OSA on insulin secretion, IR, mitochondrial function, and inflammatory markers
  - Newer and better biomarkers
  - Incidence and severity of micro- and macrovascular complications of T2DM in patients with OSA
  - Bidirectional link between T2DM and OSA

- **Intervention studies**

– Large randomized controlled trials of CPAP and other therapies in people with T2DM particularly prediabetes with special emphasis on CVD risk factors and outcomes and glycemic control are required.

  - Additional outcomes should also include oxidative stress, inflammation markers, and lipid metabolism.

– Studies on the weight loss interventions including the use of anti-obesity agents in people with OSA and T2DM should be investigated.
– Studies on combination therapies are also warranted.
– Therapies for OSA that are easier to use and cheaper than CPAP could be evaluated.

- **Economic analysis studies:** Studies evaluating the economic impact of OSA in patients with T2DM are warranted in terms of:

– Cost-effectiveness of OSA screening in T2DM-related outcomes.
– Cost-effectiveness of OSA treatment with CPAP on T2DM-related outcomes.

- **Resource development**
  Although PSG is the gold standard in the diagnosis of OSA, these studies are frequently limited by high costs and available resources such as hospital beds, waiting times, unwilling to stay overnight in the hospital for diagnosis, and labor requirements. In resource-limiting countries like India:

– A reliable but inexpensive diagnostic technique for OSA is needed in primary care settings.
– A precise and easy to handle clinical screening tools (i.e., home monitoring devices) are required to better diagnose and predict the severity of OSA, and for better risk stratification and to facilitate the efficiency of patient management.

Acknowledgments The preparation of this article was supported by ResMed India Pvt. Ltd. Priya Ganpathy, MPharm CMPP, provided medical writing assistance and Sangita Patil, PhD CMPP (SIRO Clinpharm Pvt. Ltd), provided additional editorial support. Manasi Date, PhD (SIRO Clinpharm Pvt. Ltd), provided support with literature search and data extraction.

Authorship contributions All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. International Diabetes Federation. IDF Diabetes Atlas teB, Belgium: International Diabetes Federation. 2017.
2. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. Chest. 2014;146(5):1387–94. https://doi.org/10.1378/chest.14-0970.
3. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7(8):687–98. https://doi.org/10.1016/S2213-2600(19)30198-5.
4. Raju YSSD, Yadati R, Alekhya A. Diabetes mellitus and obstructive sleep apnoea: implications for clinicians. J Clin Sci Res. 2016;5:225–33. https://doi.org/10.15380/2277-5706.JCSR.16.05.003.
5. Hla KM, Young T, Hagen EW, Stein JH, Finn LA, Nieto FJ, et al. Coronary heart disease incidence in sleep disordered breathing: the Wisconsin Sleep Cohort Study. Sleep. 2015;38(5):677–84. https://doi.org/10.5665/sleep.4654.
6. Gottlieb DJ, Yenokyan G, Newman AB, O'Connor GT, Punjabi NM, Quan SF, et al. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. Circulation. 2010;122(4):352–60. https://doi.org/10.1161/CIRCULATIONAHA.109.901801.
7. Hou H, Zhao Y, Yu W, Dong H, Xue X, Ding J, et al. Association of obstructive sleep apnea with hypertension: a systematic review and meta-analysis. J Glob Health. 2018;8(1):010405. https://doi.org/10.7189/jogh.08.010405.

8. Resnick HE, Redline S, Shahar E, Gilpin A, Newman A, Walter R, et al. Diabetes and sleep disturbances: findings from the Sleep Heart Health Study. Diabetes Care. 2003;26(3):702–9. https://doi.org/10.2337/diacare.26.3.702.
9. Huang T, Lin BM, Stampfer MJ, Tworoger SS, Hu FB, Redline S. A population-based study of the bidirectional association between obstructive sleep apnea and type 2 diabetes in three prospective U.S. cohorts. Diabetes Care. 2018;41(10):2111–9. https://doi.org/10.2337/dc18-0675.
10. Bonsignore MR, Baiamonte P, Mazzuca E, Castrogiovanni A, Marrone O. Obstructive sleep apnea and comorbidities: a dangerous liaison. Multidiscip Respir Med. 2019;14:8. https://doi.org/10.1186/s40248-019-0172-9.
11. Pillar G, Shehadeh N. Abdominal fat and sleep apnea: the chicken or the egg? Diabetes Care. 2008;31(Suppl 2):S303–9. https://doi.org/10.2337/dc08-s272.
12. Ioja SCE, Ng J, et al. Obstructive sleep apnea in adults with type 1 and type 2 diabetes: perspectives from a quality improvement initiative in a university-based diabetes center. BMJ Open Diabetes Res Care. 2017;5(1):1–5. https://doi.org/10.1136/bmjdrc-2017-000433.
13. American Diabetes Association (ADA). Standards of medical care in diabetes. Diabetes Care. 2014;37:S14–80.
14. Viswanathan V, Ramalingam IP, Ramakrishnan N. High prevalence of obstructive sleep apnea among people with type 2 diabetes mellitus in a tertiary care center. J Assoc Physicians India. 2017;65(11):38–42.
15. Singh APS, Jain J, Singh R. Polysomnographic study in diabetes mellitus in central Indian subjects. J Mahatma Gandhi Inst Med Sci. 2012;17:17–21.
16. Malik JA, Masoodi SR, Shoib S. Obstructive sleep apnea in type 2 diabetes and impact of continuous positive airway pressure therapy on glycemic control. Indian J Endocrinol Metab. 2017;21(1):106–12. https://doi.org/10.4103/2230-8210.196005.
17. Ekka RSJ, Singh C, Sen MK, Gupta A. Prevalence of obstructive sleep apnea in type 2 diabetes mellitus. 2010;5:18–26.
18. Bhimwal RKMM, Jangid R, Bhati RL. To study the prevalence of obstructive sleep apnoea in type 2 diabetes patients in Western Rajasthan, India. Int J Adv Med. 2017;4(4):894–902. https://doi.org/10.18203/2349-3933.ijam20172569.
19. Sharma SK, Katoch VM, Mohan A, Kadhiravan T, Elavarasi A, Ragesh R, et al. Consensus and evidence-based Indian initiative on obstructive sleep apnea guidelines 2014 (first edition). Lung India. 2015;32(4):422–34. https://doi.org/10.4103/0970-2113.159677.
20. Siwasaranond N, Nimitphong H, Manodpitipong A, Saetung S, Chirakalwasan N, Thakkinstian A, et al. The relationship between diabetes-related complications and obstructive sleep apnea in type 2 diabetes. J Diabetes Res. 2018;2018:9269170. https://doi.org/10.1155/2018/9269170.
21. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):144–53. https://doi.org/10.1513/pats.200707-114MG.
22. Levy P, Kohler M, McNicholas WT, Barbe F, McEvoy RD, Somers VK, et al. Obstructive sleep apnoea syndrome. Nat Rev Dis Primers. 2015;1:15015. https://doi.org/10.1038/nrdp.2015.15.
23. Laratta CR, Ayas NT, Povitz M, Pendharkar SR. Diagnosis and treatment of obstructive sleep apnea in adults. CMAJ. 2017;189(48):E1481–E8. https://doi.org/10.1503/cmaj.170296.
24. Semelka M, Wilson J, Floyd R. Diagnosis and treatment of obstructive sleep apnea in adults. Am Fam Physician. 2016;94(5):355–60.
25. Stansbury RC, Strollo PJ. Clinical manifestations of sleep apnea. J Thorac Dis. 2015;7(9):E298–310. https://doi.org/10.3978/j.issn.2072-1439.2015.09.13.
26. Amra B, Rahmati B, Soltaninejad F, Feizi A. Screening questionnaires for obstructive sleep apnea: an updated systematic review. Oman Med J. 2018;33(3):184–92. https://doi.org/10.5001/omj.2018.36.
27. Punjabi NM, Shahar E, Redline S, Gottlieb DJ, Givelber R, Resnick HE, et al. Sleep-disordered breathing, glucose intolerance, and insulin resistance: the Sleep Heart Health Study. Am J Epidemiol. 2004;160(6):521–30. https://doi.org/10.1093/aje/kwh261.
28. Bhat SUH, DeBari VA, Ahmad M, Polos PG, Chokroverty S. The utility of patient-completed and partner-completed Epworth Sleepiness Scale scores in the evaluation of obstructive sleep apnea. Sleep Breath. 2016;20(4):1347–54. https://doi.org/10.1007/s11325-016-1370-8.
29. Prasad KTSI, Agarwal R, Aggarwal AN, Behera D, Dhooria S. Assessing the likelihood of obstructive sleep apnea: a comparison of nine screening questionnaires. Sleep Breath. 2017;21(4):909–17. https://doi.org/10.1007/s11325-017-1495-4.
30. Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep. 1991;14(6):540–5. https://doi.org/10.1093/sleep/14.6.540.
31. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108(5):812–21. https://doi.org/10.1097/ALN.0b013e31816d83e4.
32. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. Br J Anaesth. 2012;108(5):768–75. https://doi.org/10.1093/bja/aes022.
33. Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med. 1999;131(7):485–91. https://doi.org/10.7326/0003-4819-131-7-199910050-00002.
34. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328(17):1230–5. https://doi.org/10.1056/NEJM199304293281704.
35. Force USPST, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, et al. Screening for obstructive sleep apnea in adults: US Preventive Services Task Force recommendation statement. JAMA. 2017;317(4):407–14. https://doi.org/10.1001/jama.2016.20325.
36. Comparative effectiveness of diagnosis and treatment of obstructive sleep apnea in adults. Comparative effectiveness review summary guides for clinicians. AHRQ comparative effectiveness reviews. Rockville (MD) 2007.
37. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005;172(12):1590–5. https://doi.org/10.1164/rccm.200504-637OC.
38. Marshall NS, Wong KK, Phillips CL, Liu PY, Knuiman MW, Grunstein RR. Is sleep apnea an independent risk factor for prevalent and incident diabetes in the Busselton Health Study? J Clin Sleep Med. 2009;5(1):15–20.
39. Rajan P, Greenberg H. Obstructive sleep apnea as a risk factor for type 2 diabetes mellitus. Nat Sci Sleep. 2015;7:113–25. https://doi.org/10.2147/NSS.S90835.
40. Qie R, Zhang D, Liu L, Ren Y, Zhao Y, Liu D, et al. Obstructive sleep apnea and risk of type 2 diabetes mellitus: a systematic review and dose-response meta-analysis of cohort studies. J Diabetes. 2019;12:455–64. https://doi.org/10.1111/1753-0407.13017.
41. Elmasry A, Janson C, Lindberg E, Gislason T, Tageldin MA, Boman G. The role of habitual snoring and obesity in the development of diabetes: a 10-year follow-up study in a male

population. J Intern Med. 2000;248(1):13–20. https://doi.org/10.1046/j.1365-2796.2000.00683.x.
42. Al-Delaimy WK, Manson JE, Willett WC, Stampfer MJ, Hu FB. Snoring as a risk factor for type II diabetes mellitus: a prospective study. Am J Epidemiol. 2002;155(5):387–93. https://doi.org/10.1093/aje/155.5.387.
43. Koren D, O'Sullivan KL, Mokhlesi B. Metabolic and glycemic sequelae of sleep disturbances in children and adults. Curr Diabetes Rep. 2015;15(1):562. https://doi.org/10.1007/s11892-014-0562-5.
44. Pugliese G, Barrea L, Laudisio D, Salzano C, Aprano S, Colao A, et al. Sleep apnea, obesity, and disturbed glucose homeostasis: epidemiologic evidence, biologic insights, and therapeutic strategies. Curr Obes Rep. 2020;9(1):30–8. https://doi.org/10.1007/s13679-020-00369-y.
45. Viswanathan V, Ramakrishnan N, Sunaina S, Vigneswari A, Satyavani K. Subjects with type 2 diabetes may have obstructive sleep apnoea even at lower BMI values. Indian J Sleep Med. 2012;7(2):45–7.
46. Reddy EV, Kadhiravan T, Mishra HK, Sreenivas V, Handa KK, Sinha S, et al. Prevalence and risk factors of obstructive sleep apnea among middle-aged urban Indians: a community-based study. Sleep Med. 2009;10(8):913–8. https://doi.org/10.1016/j.sleep.2008.08.011.
47. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284(23):3015–21. https://doi.org/10.1001/jama.284.23.3015.
48. Mok Y, Tan CW, Wong HS, How CH, Tan KL, Hsu PP. Obstructive sleep apnoea and Type 2 diabetes mellitus: are they connected? Singap Med J. 2017;58(4):179–83. https://doi.org/10.11622/smedj.2017027.
49. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004;1(3):e62. https://doi.org/10.1371/journal.pmed.0010062.
50. Foster GD, Sanders MH, Millman R, Zammit G, Borradaile KE, Newman AB, et al. Obstructive sleep apnea among obese patients with type 2 diabetes. Diabetes Care. 2009;32(6):1017–9. https://doi.org/10.2337/dc08-1776.
51. Wang X, Greer J, Porter RR, Kaur K, Youngstedt SD. Short-term moderate sleep restriction decreases insulin sensitivity in young healthy adults. Sleep Health. 2016;2(1):63–8. https://doi.org/10.1016/j.sleh.2015.11.004.
52. Khandelwal D, Dutta D, Chittawar S, Kalra S. Sleep disorders in type 2 diabetes. Indian J Endocrinol Metab. 2017;21(5):758–61. https://doi.org/10.4103/ijem.IJEM_156_17.
53. Mussa BM, Schauman M, Kumar V, Skaria S, Abusnana S. Personalized intervention to improve stress and sleep patterns for glycemic control and weight management in obese Emirati patients with type 2 diabetes: a randomized controlled clinical trial. Diabetes Metab Syndr Obes. 2019;12:991–9. https://doi.org/10.2147/DMSO.S201142.
54. Foster GD, Borradaile KE, Sanders MH, Millman R, Zammit G, Newman AB, et al. A randomized study on the effect of weight loss on obstructive sleep apnea among obese patients with type 2 diabetes: the Sleep AHEAD study. Arch Intern Med. 2009;169(17):1619–26. https://doi.org/10.1001/archinternmed.2009.266.
55. Mesman RLS, Calleja F, Hendriks G, Morolli B, Misovic B, Devilee P, et al. The functional impact of variants of uncertain significance in BRCA2. Genet Med. 2019;21(2):293–302. https://doi.org/10.1038/s41436-018-0052-2.
56. Calik MW. Treatments for obstructive sleep apnea. Journal of clinical outcomes management. J Clin Outcomes Manag. 2016;23(4):181–92.
57. Stasche N. Selective indication for positive airway pressure (PAP) in sleep-related breathing disorders with obstruction. GMS Curr Top Otorhinolaryngol Head Neck Surg. 2006;5:Doc06.
58. Sutherland K, Vanderveken OM, Tsuda H, Marklund M, Gagnadoux F, Kushida CA, et al. Oral appliance treatment for obstructive sleep apnea: an update. J Clin Sleep Med. 2014;10(2):215–27. https://doi.org/10.5664/jcsm.3460.
59. Morgenthaler TI, Aurora RN, Brown T, Zak R, Alessi C, Boehlecke B, et al. Practice parameters for the use of autotitrating continuous positive airway pressure devices for titrating pressures and treating adult patients with obstructive sleep apnea syndrome: an update for 2007. An American Academy of Sleep Medicine report. Sleep. 2008;31(1):141–7. https://doi.org/10.1093/sleep/31.1.141.
60. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath 2007;11(1):1–22. https://doi.org/10.1007/s11325-006-0084-8, 1.
61. Gagnadoux F, Fleury B, Vielle B, Petelle B, Meslier N, N'Guyen XL, et al. Titrated mandibular advancement versus positive airway pressure for sleep apnoea. Eur Respir J. 2009;34(4):914–20. https://doi.org/10.1183/09031936.00148208.
62. Dieltjens M, Vanderveken O. Oral appliances in obstructive sleep apnea. Healthcare (Basel). 2019;7(4). https://doi.org/10.3390/healthcare7040141.
63. Zaghi S, Holty JE, Certal V, Abdullatif J, Guilleminault C, Powell NB, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. JAMA Otolaryngol Head Neck Surg. 2016;142(1):58–66. https://doi.org/10.1001/jamaoto.2015.2678.
64. Remmers J, Charkhandeh S, Grosse J, Topor Z, Brant R, Santosham P, et al. Remotely controlled mandibular protrusion during sleep predicts therapeutic success with oral appliances in patients with obstructive sleep apnea. Sleep. 2013;36(10):1517–25,25A. https://doi.org/10.5665/sleep.3048.
65. Deane SA, Cistulli PA, Ng AT, Zeng B, Petocz P, Darendeliler MA. Comparison of mandibular advancement splint and tongue stabilizing device in obstructive sleep apnea: a randomized controlled trial. Sleep. 2009;32(5):648–53. https://doi.org/10.1093/sleep/32.5.648.
66. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Clin Sleep Med. 2015;11(7):773–827. https://doi.org/10.5664/jcsm.4858.
67. Li HY, Lee LA, Hsin LJ, Fang TJ, Lin WN, Chen HC, et al. Intrapharyngeal surgery with integrated treatment for obstructive sleep apnea. Biom J. 2019;42(2):84–92. https://doi.org/10.1016/j.bj.2019.02.002.
68. Kahn SE, Hull RL, Utzschneider KM. Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature. 2006;444(7121):840–6. https://doi.org/10.1038/nature05482.
69. Cizza G, de Jonge L, Piaggi P, Mattingly M, Zhao X, Lucassen E, et al. Neck circumference is a predictor of metabolic syndrome and obstructive sleep apnea in short-sleeping obese men and women. Metab Syndr Relat Disord. 2014;12(4):231–41. https://doi.org/10.1089/met.2013.0093.
70. Jehan S, Myers AK, Zizi F, Pandi-Perumal SR, Jean-Louis G, McFarlane SI. Obesity, obstructive sleep apnea and type 2 diabetes mellitus: epidemiology and pathophysiologic insights. Sleep Med Disord. 2018;2(3):52–8.
71. Doumit J, Prasad B. Sleep apnea in type 2 diabetes. Diabetes Spectr. 2016;29(1):14–9. https://doi.org/10.2337/diaspect.29.1.14.
72. Vgontzas AN, Papanicolaou DA, Bixler EO, Kales A, Tyson K, Chrousos GP. Elevation of plasma cytokines in disorders of excessive daytime sleepiness: role of sleep disturbance and obesity. J

Clin Endocrinol Metab. 1997;82(5):1313–6. https://doi.org/10.1210/jcem.82.5.3950.
73. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415–28. https://doi.org/10.1016/S0140-6736(05)66378-7.
74. Xu S, Wan Y, Xu M, Ming J, Xing Y, An F, et al. The association between obstructive sleep apnea and metabolic syndrome: a systematic review and meta-analysis. BMC Pulm Med. 2015;15:105. https://doi.org/10.1186/s12890-015-0102-3.
75. Basoglu OK, Sarac F, Sarac S, Uluer H, Yilmaz C. Metabolic syndrome, insulin resistance, fibrinogen, homocysteine, leptin, and C-reactive protein in obese patients with obstructive sleep apnea syndrome. Ann Thorac Med. 2011;6(3):120–5. https://doi.org/10.4103/1817-1737.82440.
76. Soin D, Kumar PA, Chahal J, Chawla SPS, Kaur S, Garg R, et al. Evaluation of obstructive sleep apnea in metabolic syndrome. J Family Med Prim Care. 2019;8(5):1580–6. https://doi.org/10.4103/jfmpc.jfmpc_175_19.
77. Jun J, Polotsky VY. Metabolic consequences of sleep-disordered breathing. ILAR J. 2009;50(3):289–306. https://doi.org/10.1093/ilar.50.3.289.
78. SM TEaM. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. Proc Am Thorac Soc. 2008;5:207–17. https://doi.org/10.1513/pats.200708-139MG.
79. Balkau B, Vol S, Loko S, Andriamboavonjy T, Lantieri O, Gusto G, et al. High baseline insulin levels associated with 6-year incident observed sleep apnea. Diabetes Care. 2010;33(5):1044–9. https://doi.org/10.2337/dc09-1901.
80. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the sleep heart health study. Arch Intern Med. 2005;165(20):2408–13. https://doi.org/10.1001/archinte.165.20.2408.
81. Licinio J, Wong ML. Sequence and function in pharmacogenomics. Pharm J. 2003;3(3):123. https://doi.org/10.1038/sj.tpj.6500185.
82. Tantucci C, Scionti L, Bottini P, Dottorini ML, Puxeddu E, Casucci G, et al. Influence of autonomic neuropathy of different severities on the hypercapnic drive to breathing in diabetic patients. Chest. 1997;112(1):145–53. https://doi.org/10.1378/chest.112.1.145.
83. Kent BD, Grote L, Ryan S, Pepin JL, Bonsignore MR, Tkacova R, et al. Diabetes mellitus prevalence and control in sleep-disordered breathing: the European Sleep Apnea Cohort (ESADA) study. Chest. 2014;146(4):982–90. https://doi.org/10.1378/chest.13-2403.
84. Papanas N, Steiropoulos P, Nena E, Tzouvelekis A, Maltezos E, Trakada G, et al. HbA1c is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. Vasc Health Risk Manag. 2009;5:751–6. https://doi.org/10.2147/vhrm.s7057.
85. Pillai AWG, Gunathilake W, Idris I. Control in patients with type 2 diabetes prior to continuous positive airway pressure treatment. Diabetes Technol Ther. 2011;13:945–9. https://doi.org/10.1089/dia.2011.0005.
86. 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(5):507–13. https://doi.org/10.1164/rccm.200909-1423OC.
87. Tsai YW, Kann NH, Tung TH, Chao YJ, Lin CJ, Chang KC, et al. Impact of subjective sleep quality on glycemic control in type 2 diabetes mellitus. Fam Pract. 2012;29(1):30–5. https://doi.org/10.1093/fampra/cmr041.
88. Tahrani AA. Obstructive sleep apnoea in diabetes: does it matter? Diab Vasc Dis Res. 2017;14(5):454–62. https://doi.org/10.1177/1479164117714397.
89. Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, et al. Obstructive sleep apnea and retinopathy in patients with type 2 diabetes. A longitudinal study. Am J Respir Crit Care Med. 2017;196(7):892–900. https://doi.org/10.1164/rccm.201701-0175OC.
90. Mason RH, West SD, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, et al. High prevalence of sleep disordered breathing in patients with diabetic macular edema. Retina. 2012;32(9):1791–8. https://doi.org/10.1097/IAE.0b013e318259568b.
91. Fujihara K, Kodama S, Horikawa C, Yoshizawa S, Sugawara A, Hirasawa R, et al. The relationship between diabetic neuropathy and sleep apnea syndrome: a meta-analysis. Sleep Disord. 2013;2013:150371. https://doi.org/10.1155/2013/150371.
92. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf QA, et al. Obstructive sleep apnea and diabetic nephropathy: a cohort study. Diabetes Care. 2013;36(11):3718–25. https://doi.org/10.2337/dc13-0450.
93. Seicean S, Strohl KP, Seicean A, Gibby C, Marwick TH. Sleep disordered breathing as a risk of cardiac events in subjects with diabetes mellitus and normal exercise echocardiographic findings. Am J Cardiol. 2013;111(8):1214–20. https://doi.org/10.1016/j.amjcard.2012.12.053.
94. Rivas M, Ratra A, Nugent K. Obstructive sleep apnea and its effects on cardiovascular diseases: a narrative review. Anatol J Cardiol. 2015;15(11):944–50. https://doi.org/10.5152/AnatolJCardiol.2015.6607.
95. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283(14):1829–36. https://doi.org/10.1001/jama.283.14.1829.
96. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, et al. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med. 1997;157(15):1746–52.
97. Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M, Stubbs M. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. Sleep. 2008;31(6):795–800. https://doi.org/10.1093/sleep/31.6.795.
98. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034–41. https://doi.org/10.1056/NEJMoa043104.
99. Tung P, Levitzky YS, Wang R, Weng J, Quan SF, Gottlieb DJ, et al. Obstructive and central sleep apnea and the risk of incident atrial fibrillation in a community cohort of men and women. J Am Heart Assoc. 2017;6(7). https://doi.org/10.1161/JAHA.116.004500.
100. Kylintireas I, Craig S, Nethononda R, Kohler M, Francis J, Choudhury R, Stradling J, Neubauer S. Atherosclerosis and arterial stiffness in obstructive sleep apnea–a cardiovascular magnetic resonance study. Atherosclerosis. 2012;222(2):483–489. https://doi.org/10.1016/j.atherosclerosis.2012.03.036.
101. Kawano Y, Tamura A, Kadota J. Association between the severity of obstructive sleep apnea and the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol. Metabolism. 2012;61(2):186–92. https://doi.org/10.1016/j.metabol.2011.06.004.
102. Doonan RJ, Scheffler P, Lalli M, Kimoff RJ, Petridou ET, Daskalopoulos ME, et al. Increased arterial stiffness in obstructive sleep apnea: a systematic review. Hypertens Res. 2011;34(1):23–32. https://doi.org/10.1038/hr.2010.200.
103. Selim BJ, Koo BB, Qin L, Jeon S, Won C, Redeker NS, et al. The association between nocturnal cardiac arrhythmias and sleep-disordered breathing: the DREAM study. J Clin Sleep Med. 2016;12(6):829–37. https://doi.org/10.5664/jcsm.5880.

104. Banno K, Ramsey C, Walld R, Kryger MH. Expenditure on health care in obese women with and without sleep apnea. Sleep. 2009;32(2):247–52. https://doi.org/10.1093/sleep/32.2.247.
105. Seetho IWWJ. Screening for obstructive sleep apnoea in obesity and diabetes – potential for future approaches. Eur J Clin Investig. 2013;43(6):640–55.
106. Misra A, Chowbey P, Makkar BM, Vikram NK, Wasir JS, Chadha D, et al. Consensus statement for diagnosis of obesity, abdominal obesity and the metabolic syndrome for Asian Indians and recommendations for physical activity, medical and surgical management. J Assoc Physicians India. 2009;57:163–70.
107. Edmonds PJ, Gunasekaran K, Edmonds LC. Neck grasp predicts obstructive sleep apnea in type 2 diabetes mellitus. Sleep Disord. 2019;2019:3184382. https://doi.org/10.1155/2019/3184382.
108. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263–76.
109. Foroughi M, Razavi H, Malekmohammad M, Adimi Naghan P, Jamaati H. Diagnosis of obstructive sleep apnea syndrome in adults: a brief review of existing data for practice in Iran. Tanaffos. 2016;15(2):70–4.
110. Weinstock TG, Wang X, Rueschman M, Ismail-Beigi F, Aylor J, Babineau DC, et al. A controlled trial of CPAP therapy on metabolic control in individuals with impaired glucose tolerance and sleep apnea. Sleep. 2012;35(5):617–25B. https://doi.org/10.5665/sleep.1816.
111. Pamidi S, Wroblewski K, Stepien M, Sharif-Sidi K, Kilkus J, Whitmore H, et al. Eight hours of nightly continuous positive airway pressure treatment of obstructive sleep apnea improves glucose metabolism in patients with Prediabetes. A randomized controlled trial. Am J Respir Crit Care Med. 2015;192(1):96–105. https://doi.org/10.1164/rccm.201408-1564OC.
112. 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(11):969–74. https://doi.org/10.1136/thx.2006.074351.
113. Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. J Clin Endocrinol Metab. 2012;97(11):4212–8. https://doi.org/10.1210/jc.2012-2107.
114. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, et al. The effect of treatment of obstructive sleep apnea on glycemic control in type 2 diabetes. Am J Respir Crit Care Med. 2016;194(4):486–92. https://doi.org/10.1164/rccm.201511-2260OC.
115. Martinez-Ceron E, Barquiel B, Bezos AM, Casitas R, Galera R, Garcia-Benito C, et al. Effect of continuous positive airway pressure on glycemic control in patients with obstructive sleep apnea and type 2 diabetes. A randomized clinical trial. Am J Respir Crit Care Med. 2016;194(4):476–85. https://doi.org/10.1164/rccm.201510-1942OC.
116. Mokhlesi B, Grimaldi D, Beccuti G, Abraham V, Whitmore H, Delebecque F, et al. Effect of one week of 8-hour nightly continuous positive airway pressure treatment of obstructive sleep apnea on glycemic control in type 2 diabetes: a proof-of-concept study. Am J Respir Crit Care Med. 2016;194(4):516–9. https://doi.org/10.1164/rccm.201602-0396LE.
117. Morariu EM, Chasens ER, Strollo PJ Jr, Korytkowski M. Effect of continuous positive airway pressure (CPAP) on glycemic control and variability in type 2 diabetes. Sleep Breath. 2017;21(1):145–7. https://doi.org/10.1007/s11325-016-1388-y.
118. Lam JCM, Lai AYK, Tam TCC, Yuen MMA, Lam KSL, Ip MSM. CPAP therapy for patients with sleep apnea and type 2 diabetes mellitus improves control of blood pressure. Sleep Breath. 2017;21(2):377–86. https://doi.org/10.1007/s11325-016-1428-7.
119. Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363(9403):157–63. https://doi.org/10.1016/S0140-6736(03)15268-3.
120. Chawla R, Madhu SV, Makkar BM, Ghosh S, Saboo B, Kalra S, et al. RSSDI-ESI clinical practice recommendations for the management of type 2 diabetes mellitus 2020. Indian J Endocrinol Metab. 2020;24(1):1–122. https://doi.org/10.4103/ijem.IJEM_225_20.
121. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical practice guideline for diagnostic testing for adult obstructive sleep apnea: an Ac clinical practice guideline. J Clin Sleep Med. 2017;13(3):479–504. https://doi.org/10.5664/jcsm.6506.
122. Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. Sleep. 2005;28(1):113–21. https://doi.org/10.1093/sleep/28.1.113.
123. Levendowski DJ, Zack N, Rao S, Wong K, Gendreau M, Kranzler J, et al. Assessment of the test-retest reliability of laboratory polysomnography. Sleep Breath. 2009;13(2):163–7. https://doi.org/10.1007/s11325-008-0214-6.
124. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007;3(7):737–47.
125. El Shayeb M, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. CMAJ. 2014;186(1):E25–51. https://doi.org/10.1503/cmaj.130952.
126. Calleja JM, Esnaola S, Rubio R, Duran J. Comparison of a cardiorespiratory device versus polysomnography for diagnosis of sleep apnoea. Eur Respir J. 2002;20(6):1505–10. https://doi.org/10.1183/09031936.02.00297402.
127. Kingshott RN, Gahleitner F, Elphick HE, Gringras P, Farquhar M, Pickering RM, et al. Cardiorespiratory sleep studies at home: experience in research and clinical cohorts. Arch Dis Child. 2019;104(5):476–81. https://doi.org/10.1136/archdischild-2018-315676.
128. Tietjens JR, Claman D, Kezirian EJ, De Marco T, Mirzayan A, Sadroonri B, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. J Am Heart Assoc. 2019;8(1):e010440. https://doi.org/10.1161/JAHA.118.010440.
129. Ashrafian H, Toma T, Rowland SP, Harling L, Tan A, Efthimiou E, et al. Bariatric surgery or non-surgical weight loss for obstructive sleep apnoea? A systematic review and comparison of meta-analyses. Obes Surg. 2015;25(7):1239–50. https://doi.org/10.1007/s11695-014-1533-2.
130. Kuna ST, Reboussin DM, Borradaile KE, Sanders MH, Millman RP, Zammit G, et al. Long-term effect of weight loss on obstructive sleep apnea severity in obese patients with type 2 diabetes. Sleep. 2013;36(5):641–9A. https://doi.org/10.5665/sleep.2618.
131. Gaisl T, Haile SR, Thiel S, Osswald M, Kohler M. Efficacy of pharmacotherapy for OSA in adults: a systematic review and network meta-analysis. Sleep Med Rev. 2019;46:74–86. https://doi.org/10.1016/j.smrv.2019.04.009.
132. Ravesloot MJL, White D, Heinzer R, Oksenberg A, Pepin JL. Efficacy of the new generation of devices for positional therapy for patients with positional obstructive sleep apnea: a systematic

review of the literature and meta-analysis. J Clin Sleep Med. 2017;13(6):813–24. https://doi.org/10.5664/jcsm.6622.
133. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, et al. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol. 2017;69(7):841–58. https://doi.org/10.1016/j.jacc.2016.11.069.
134. Young T, Finn L, Peppard PE, Szklo-Coxe M, Austin D, Nieto FJ, et al. Sleep disordered breathing and mortality: eighteen-year follow-up of the Wisconsin sleep cohort. Sleep. 2008;31(8):1071–8.
135. Rabelo Guimaraes Mde L, Hermont AP. Sleep apnea and occupational accidents: are oral appliances the solution? Indian J Occup Environ Med. 2014;18(2):39–47. https://doi.org/10.4103/0019-5278.146887.
136. Sutherland K, Deane SA, Chan AS, Schwab RJ, Ng AT, Darendeliler MA, et al. Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. Sleep. 2011;34(4):469–77. https://doi.org/10.1093/sleep/34.4.469.
137. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130(3):576–84. https://doi.org/10.1542/peds.2012-1671.