International Diabetes Federation

## Report

# Sleep-disordered breathing and type 2 diabetes A report from the International Diabetes Federation Taskforce on Epidemiology and Prevention

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## ARTICLE INFO

## ABSTRACT

Sleep-disordered breathing (SDB) has been associated with insulin resistance and glucose intolerance, and is frequently found in people with type 2 diabetes. SDB not only causes poor sleep quality and daytime sleepiness, but has clinical consequences, including hypertension and increased risk of cardiovascular disease. In addition to supporting the need for further research into the links between SDB and diabetes, the International Diabetes Federation Taskforce on Epidemiology and Prevention strongly recommends that health professionals working in both type 2 diabetes and SDB adopt clinical practices to ensure that a patient presenting with one condition is considered for the other.

## 1. Introduction

Sleep-disordered breathing (SDB) is commonly found in patients with type 2 diabetes [1]. Recent research demonstrates the likelihood of a relationship between the two conditions independent of obesity [2]. Irrespective of the independence of relationship, the observed association of SDB with type 2 diabetes has important clinical, epidemiological

and public health implications. SDB is increasingly considered as a potential therapeutic target for either primary or secondary prevention of cardiovascular disease (CVD). This is particularly relevant in the context of coexisting type 2 diabetes, when patients are already at significant risk of CVD.

While the enormity of the type 2 diabetes epidemic is well recognised, disorders of breathing during sleep are not, in spite of the significant contribution they make to the burden of disease in individuals and the financial burden on communities.

Therefore, the need exists for a global, multidisciplinary approach to raise awareness, improve clinical practice and coordinate research efforts to better understand the links between SDB and type 2 diabetes. The International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention convened a Working Group in February 2007 to review the subject, resulting in this discussion paper in recognition of the imperative to take action.

## 2. Obstructive sleep apnoea

### 2.1. Definition

The term SDB encompasses a range of breathing abnormalities that occur during sleep. These include obstructive sleep apnoea (OSA), central sleep apnoea and periodic breathing. This report deals only with OSA, the most common form of SDB. The clinical syndrome of sleep apnoea is defined as the presence of abnormal breathing in sleep along with daytime symptoms, particularly excessive daytime sleepiness [3]. OSA is characterized by repeated episodes of upper airway collapse, leading to apnoeas (cessation of airflow ≥10 s) or hypopnoeas (decrease in airflow ≥10 s associated with either an oxyhaemoglobin desaturation or an arousal detected by electroencephalography) [4].

### 2.2. Clinical features

The clinical picture (Table 1) encompasses three characteristic features, which result directly from obstructed breathing during sleep. There is also a range of other symptoms, and a number of associated clinical disorders that are seen more commonly in those with OSA than would be expected by chance.

### 2.3. Diagnosis

1. *Signs and symptoms*: Assessment of the presence of the characteristic features (Table 1) can be augmented by the use of questionnaires (e.g. Epworth Sleepiness Scale [5], Berlin Questionnaire [6] and clinical examination including neck circumference and examination of the upper airway (looking for tonsillar enlargement, micrognathia and oropharyngeal crowding).
2. *Investigations*: The gold standard diagnostic study is polysomnography (PSG)—an inpatient study that measures physiological signals of sleep, respiratory effort, oro-nasal airflow and oxyhaemoglobin desaturation. However, other simpler methods are also available. These include over-

| Table 1 – Clinical features of SDB |
|---|
| Characteristic features |
|   A history of habitual snoring |
|   A record of witnessed apnoeas |
|   Excessive daytime sleepiness |
| Associated symptoms |
|   Fatigue/loss of energy |
|   Irritability |
|   Poor memory |
|   Depression |
|   Personality change |
|   Morning headaches |
|   Sexual dysfunction |
|   Nocturia |
| Clinical associations |
|   Hypertension |
|   Metabolic syndrome |
|   Type 2 diabetes |
|   Cardiovascular disease |
|   Obesity |

night oximetry in conjunction with measurement of either respiratory effort or respiratory flow, which can be carried out at home [7]. Irrespective of the method used, the number of apnoeas and hypopnoeas during sleep is used as a metric for defining OSA. Commonly used indices of OSA include the apnoea–hypopnoea index (AHI) (defined as the mean number of apnoea and hypopnoea episodes per hour of sleep) and the oxygen desaturation index (ODI) (the mean number of oxygen desaturations (3–4% or more below the baseline level per hour of sleep). For each of these scores, the following categories apply [8,9]:

- <5 normal;
- 5–15 mild;
- 15–30 moderate;
- ≥30 severe.

### 2.4. Epidemiology

There have been many studies of the overall prevalence of OSA in adult populations, with some variability of results, with the variability largely due to differences in disease definition and measurement parameters [3].

OSA based on overnight polysomnography has been noted in up to 9% of women and 24% of men [10]. In studies in which the diagnosis required the presence of symptoms and signs in addition to PSG findings (and so excluding those with asymptomatic OSA), lower prevalences have been reported: 1–5% in men and 1–3% in women [3,10].

Cross-sectional surveys show that obesity (particularly central obesity) is the strongest risk factor for OSA; male gender, age and ethnicity also contribute [11]. Some studies have suggested that Hispanic and African-American populations may be at greater risk than Europids [12–14]. Other studies have shown no increase in African-Americans, although the increased risk may still be present in the under 25s [15], and disease severity may be worse in the African-American elderly [12]. Studies of Chinese [16,17] Indian [18,19] and Korean groups [20] show similar a prevalence of OSA as in

Europeans despite obesity rates being lower; possibly due to differences in craniofacial features.

### 2.5.    Treatment

Different treatment options exist for OSA according to the degree of disease severity.

1. *Lifestyle modification*: Weight loss should be recommended for obese and overweight patients regardless of other therapeutic interventions. Alcohol and sedative medication have been suggested by some, but not all, studies to worsen the tendency of the upper airway to collapse, and hence avoidance of these may be beneficial.
2. *Continuous positive airways pressure* (CPAP): This is a widely used treatment, and is particularly beneficial in moderate–severe OSA. A mask is worn over the nose each night during sleep, delivering continuous positive pressure to maintain patency of the airway. The pressure delivered is titrated to individual requirements.
3. *Oral appliances*: These devices may be beneficial, particularly in mild OSA [9]. A plastic mouthpiece is custom-fitted to increase upper airway dimensions and decrease the propensity for airway collapse during sleep.
4. *Surgery*: In cases with remedial upper airway obstruction, surgical interventions may be helpful. These include removal of enlarged tonsils and adenoids or nasal polyps and certain orthodontic and maxillofacial procedures.

### 2.6.    Economics

Estimates of the medical costs of untreated OSA in the United States are US$ 3.4 billion/year [21]. Over 80% of patients with moderate to severe OSA go undiagnosed [22], and contribute to significant usage of medical services. Patients with OSA may access up to twice as many healthcare resources as healthy subjects, prior to correct evaluation of their condition, and subsequent diagnosis and treatment of OSA leads to a reduction in healthcare utilisation [23].

The total economic impact of OSA is far greater than given by the direct medical costs, as there are substantial indirect financial costs related to sleepiness-associated accident risk and productivity losses and non-financial costs related to disability [24].

## 3.    Links between OSA and disorders of glucose metabolism

There has long been a recognized association between type 2 diabetes and OSA, and there is emerging evidence that this relationship is likely to be at least partially independent of adiposity [25,1,2].

Cross-sectional estimates from clinic populations and population studies suggest that up to 40% of patients with OSA will have diabetes [26,27], but the incidence of new diabetes in patients with OSA is not known. Likewise, in patients who are known to have diabetes, the prevalence of OSA may be up to 23% [1], and the prevalence of some form of SDB may be as high as 58% [28].

### 3.1.    Effects of OSA on the development of type 2 diabetes

Early studies indicated a possible causal association between the presence of OSA and development of type 2 diabetes. However, many of the studies showed significant limitations including small sample size, highly select populations, inadequate adjustment for confounders and use of surrogate measures such as snoring to assess OSA. The observational studies to date can be divided into those using self-reported surrogate parameters for the presence of OSA, and those using objective measurement with PSG.

1. *Self-report sleep parameters and type 2 diabetes*: Two large studies [29,30] found snoring to be a risk factor for the development of diabetes over 10 years independent of confounding factors. Other subjective measures shown to be linked to incident type 2 diabetes have included reported difficulty falling asleep, the need for sedatives to fall asleep, and difficulty maintaining sleep [31–33]. These relationships between self-report sleep parameters and risk of diabetes may be less pronounced in women than in men [33]. A number of studies also indicate a link between both short and long duration of sleep and the subsequent development of diabetes [34].
2. *Polysomnography-defined OSA and type 2 diabetes*: A study of French men referred for assessment of sleep showed those with OSA (AHI > 10) were significantly more likely to have impaired glucose tolerance (IGT) and diabetes than were those without OSA [26]. The Sleep Heart Health Study [2] showed a significant association between oxygen desaturation during sleep and elevated fasting and 2-h plasma glucose concentrations during an oral glucose tolerance test (OGTT). The severity of the OSA was also associated with the degree of insulin resistance after adjustment for obesity. The Wisconsin Sleep Study ($n = 1387$) showed a significant cross-sectional association between OSA and type 2 diabetes for all degrees of OSA, which was preserved for those with moderate–severe OSA after adjustment for obesity (OR = 2.3) [35]. The longitudinal data from the same study, however, showed that after adjusting for obesity, OSA at baseline was not a significant predictor of the development of diabetes over 4 years.

Further longitudinal studies are required before definitive conclusions can be reached about causality (see Section 8).

### 3.2.    Effects of OSA on glycaemic control in people with existing type 2 diabetes

Among those with diabetes, sleep duration and quality have been shown to be significant predictors of HbA1c [36]. Some studies of the effect of CPAP treatment for OSA on carbohydrate metabolism have shown improvements in insulin sensitivity [37], glycaemic control [38] and HbA1c [38,39]. However, several recent controlled trials have not shown benefit in patients with metabolic syndrome or diabetes [40–42] (see Section 5.2.1).

### 3.3. Effects of OSA on components of the metabolic syndrome

Features of the metabolic syndrome are more prevalent in patients with OSA, independent of obesity and a correlation has been suggested between the presence of the metabolic syndrome and increased OSA severity [25,43]. Conversely, subjects with the metabolic syndrome have also been shown to have an increased risk of having OSA (OR = 2.62 (1.37–4.50)) [44].

### 3.4. Pathophysiology—OSA and impaired glucose metabolism

There are a number of proposed causal pathways linking OSA with type 2 diabetes (see Fig. 1).

There is evidence that the physiologic stress imposed by intermittent hypoxia [45–47] and/or sleep fragmentation [48,49] may be involved in the pathogenesis of insulin resistance via one or more of the following biological mechanisms (see Fig. 1):

1. Sympathetic nervous system activation.

   The sympathetic nervous system plays a central role in the regulation of glucose and fat metabolism [50]. OSA has been shown to increase sympathetic activity not only during sleep, but also when subjects are awake [51,52]. Sympathetic activation is thought to be predominantly a result of nocturnal hypoxia [53,54]. However, the repeated arousal from sleep that follows each obstructive breathing event is likely to exacerbate this effect [55,56].

2. Direct effects of hypoxia.

   The temporal alliance between oxyhaemoglobin desaturation and arousal from sleep in OSA poses the challenge of segregating their independent pathophysiologic effects. Recent work in normal human subjects, however, has shown that sleep disruption [57] and intermittent hypoxia [58] can each decrease insulin sensitivity and worsen glucose tolerance [57–59]. Furthermore, animal data show that intermittent hypoxia during waking hours (i.e. not accompanied by arousals or other sleep disturbances) leads to a reduction in insulin sensitivity [59].

3. Hypothalamic–pituitary–adrenal (HPA) dysfunction.

   Hypoxia and sleep fragmentation may lead to activation of the HPA axis and excessive and/or an abnormal pattern of elevation of cortisol levels [60,61], with the potential for negative consequences on insulin sensitivity and insulin secretion.

4. Systemic inflammation.

   OSA patients have been shown to have higher levels of inflammatory markers [62–64] as well as showing increased monocyte and lymphocyte activation with evidence that these changes are independent of adiposity [65]. These effects are thought to be largely due to the effects of intermittent hypoxia, but sympathetic activation probably also plays a role.

5. Adipokines.

   Leptin levels have been shown to be higher [66] and adiponectin levels to be lower in patients with OSA. However, the data are inconsistent as to whether this is independent of obesity [67] and whether the levels improve with treatment of OSA, making it uncertain as to whether or not they are involved in causal pathways.

6. Sleep architecture.

   A recent study [68] examined selective suppression of slow-wave sleep (a phase of sleep thought to be the most 'restorative' stage) in healthy young adults, without affecting sleep duration or causing hypoxia. The intervention markedly reduced insulin sensitivity and led to an impairment of glucose tolerance.

The fatigue and somnolence resulting from OSA may reduce physical activity, and so lead to an increased risk of diabetes, thus providing another potential mechanistic link by which OSA may lead to diabetes.

It is also worthy of note that the autonomic dysfunction resulting from diabetes may increase the risk of OSA. The
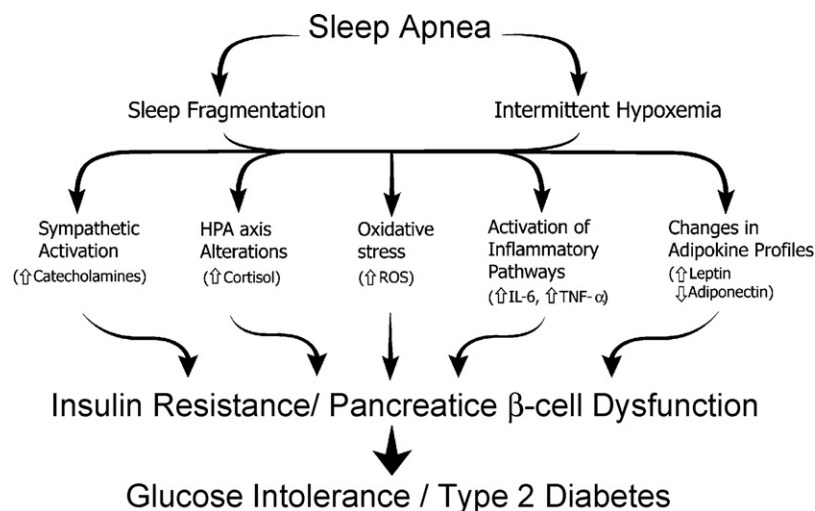


Fig. 1 – Potential mechanisms linking sleep apnoea to glucose intolerance.

Sleep Heart Health Study has shown that periodic breathing (a central abnormality of breathing during sleep), but not OSA, is more common in those with than without diabetes [28]. In a much smaller study [69], diabetic autonomic neuropathy was associated with increased central and decreased peripheral chemosensitivity to carbon dioxide. 30% of those with autonomic neuropathy exhibited obstructive sleep apnoea/hypopnoea, but no periodic breathing or central sleep apnoea was seen. Clearly, further studies are needed to clarify the role of autonomic neuropathy in abnormalities of upper airway collapsibility and control of breathing during sleep.

## 4. Links between OSA and cardiovascular disorders

OSA is associated with a variety of cardiovascular conditions ranging from hypertension to heart failure [69,70], and OSA has become increasingly considered as a potential therapeutic target for either primary or secondary prevention of CVD.

### 4.1. Hypertension

OSA has been definitively shown to be an independent risk factor for the development of hypertension [71]. In this study, patients with mild to moderate OSA (AHI 5–14.9) were twice as likely to develop hypertension as were those without OSA. The odds ratio rose to 2.89 in patients with severe OSA (AHI > 15).

Recent guidelines recommend screening for the presence of OSA in patients with refractory hypertension [72].

### 4.2. Cardiovascular disease

In one cross-sectional study [73], OSA was associated with a range of manifestations of CVD (stroke, heart failure, ischaemic heart disease). The prevalence of CVD increased progressively with increasing AHI, with multivariable-adjusted relative odds (95% CI) of prevalent CVD for the second, third, and fourth quartiles of the AHI (versus the first) of 0.98 (0.77–1.24), 1.28 (1.02–1.61), and 1.42 (1.13–1.78), respectively.

Other studies show that OSA is associated with myocardial infarction and in those with known coronary disease, patients with OSA have an increased risk of cardiovascular events and death [74,75]. Cardiac arrhythmias and sudden cardiac death have also been shown to be more common in patients with OSA [76–79].

### 4.3. Pathophysiology—OSA and cardiovascular disease

A variety of mechanisms and pathways may promote the development of CVD in those with OSA.

1. Mechanical changes.
   With each apnoeic or hypopnoeic episode, there is exaggerated negative pleural pressure. This may impact upon cardiac performance and induce shear stress on the vasculature [80].

2. Intermittent hypoxia and oxidative stress.
   Hypoxia is a strong stimulus for acute elevation of blood pressure. In chronic hypoxia and hypercarbia, chemoreceptors may undergo long-term adaptation and play a major role in elevating baseline blood pressure [81,82]. In the short-term, both chemoreceptor and sympathetically activated processes may mediate the increases in blood pressure associated with simulated or spontaneous apnoeas [83–86].
   Evidence suggests that recurrent intermittent hypoxia–reoxygenation in OSA may lead to a state of oxidative stress [87–89] and activation of inflammatory transcription pathways [88,89].

3. Systemic inflammation, vasoactive mediators, and endothelial dysfunction.
   Adverse changes in circulating levels of many vasoactive or inflammatory mediators including nitric oxide, interleukin-6, tumour necrosis factor, C-reactive protein, and platelet activation and coagulation factors have been described in OSA [87,89–100].

4. Sympathetic activation.
   Repeated oscillations in blood pressure following breathing events in OSA may reset central baroreceptors making them less sensitive, thus leading to persistent elevation of blood pressure [72]. Furthermore, OSA increases catecholamine levels, which may increase the risk of CVD events and heart failure [54].

5. Effects on lipids.
   Evidence of contribution of OSA towards modification of circulating levels of lipids is conflicting [99,100]. Animal studies have shown that intermittent hypoxia upregulates genes of lipid biosynthesis [101], and that dyslipidemia and lipid peroxidation are dependent on the severity of the hypoxia [102]. Both increased levels of oxidized LDL, and dysfunction of HDL have been described in OSA [89,103].

6. Physical inactivity.
   The links described above between physical inactivity and both OSA and diabetes are also likely to apply to CVD.

## 5. Impact of treatment of OSA

### 5.1. Benefits of weight loss

Weight loss (either from dietary or surgical intervention) has been associated with improvements in AHI [104]. However, nearly all weight loss studies are observational, with minimal data from controlled trials. Nevertheless, weight loss is a primary treatment strategy for OSA in an overweight or obese patient. As weight is lost, patients may notice reduced symptoms of OSA including more energy, improved social interaction, cognition, and work performance, fewer accidents and decreased erectile dysfunction. Additionally, reduction of daytime fatigue may lead to increased physical activity and subsequent benefits on glucose metabolism, as well as

enabling achievement and maintenance of a healthy body weight. Such outcomes have not been formally studied, and there is an urgent need to do so (see Section 8).

### 5.2. Effects of continuous positive airway pressure treatment of OSA

#### 5.2.1. Impacts on glucose metabolism

A number of studies have been conducted to determine if treatment of OSA with CPAP improves glucose metabolism and glycaemic control. Low patient numbers and lack of adequate control subjects limited initial studies, the majority of which showed no significant effects [91,105–112]. More recently, a number of more rigorously designed studies have been conducted, with mixed results. One study in non-diabetic subjects demonstrated a significant improvement in insulin sensitivity after two nights of CPAP treatment and this effect was preserved after 3 months [113]. The improvement in insulin sensitivity was seen mostly in patients with BMI $< 30 \, kg/m^2$. However, a randomized-controlled crossover study in a non-diabetic, but quite obese, population showed no effects of CPAP (versus sham CPAP) on fasting serum glucose, insulin levels or insulin sensitivity [40]. Studies of OSA treatment in type 2 diabetes have also been equivocal. One small study showed a significant improvement in insulin sensitivity after 3 months, but no effect on HbA1c [37]. A recent randomized controlled trial showed no change in insulin resistance or HbA1c after 3 months of CPAP treatment [41]. However, other studies have shown a significant reduction of HbA1c in patients with suboptimal diabetes control [38,39]. A recent observational study has shown that obese patients with OSA had reductions in visceral fat and leptin levels, but not in blood glucose or insulin resistance after 12 weeks of CPAP. The benefits were seen in those who used CPAP for >4 h/night, but not in those with less regular CPAP use [42].

#### 5.2.2. Impacts on cardiovascular disease

Treatment of OSA with CPAP has been shown to impact on a range of cardiovascular measures [114,115]. In resistant hypertension, guidelines recommend the investigation for and treatment of any existing OSA [70]. Treatment of OSA with CPAP has been shown to reduce ventricular ectopy and may improve cardiovascular outcomes in patients with heart failure [116].

## 6. Potential benefits of screening

### 6.1. Screening patients with OSA for metabolic disorders

Metabolic disease, including type 2 diabetes, is very common in patients with OSA. Treatment is available that is likely to reduce the risk of micro- and macrovascular complications. The screening tests (waist measurement, blood pressure measurement and fasting lipids and glucose [followed with an OGTT, where appropriate]) are inexpensive and easy to conduct. Monitoring of metabolic parameters is an essential part of the care of patients with OSA.

### 6.2. Screening patients with type 2 diabetes for OSA

Screening questionnaires for OSA have relatively poor sensitivity and specificity, and they have not been validated in diabetic populations, where the prevalence of fatigue and daytime sleepiness may be increased, even in the absence of OSA [117]. However, since those patients with symptomatic daytime sleepiness are those who stand to benefit most from treatment of OSA (as well as the most likely to comply with treatment in the long term), it may be considered worthwhile to target these patients specifically. Currently, there is inadequate evidence to support screening on the basis of an expectation that treatment will improve metabolic parameters, other than blood pressure. Thus, a practical approach until more research information is available might be to investigate only those patients with classical symptoms, such as witnessed apnoeas, heavy snoring or daytime sleepiness, despite the fact that some patients with OSA will not be identified this way. Those with refractory hypertension should also be considered for screening, as treating undiagnosed OSA may improve blood pressure [70].

Although identification of OSA has long relied on the use of an in-laboratory polysomnogram, diagnostic testing is expensive and may not be accessible in all clinical settings. Evidence from a study of 59 people with diabetes, who each had polysomnography and an assessment with a portable monitoring (PM) unit, showed that using an AHI cut-off of 15, over 90% of individuals were correctly classified by PM [118]. One screening strategy uses a two-stage approach in which a structured questionnaire (e.g., the Berlin questionnaire) is used in the first stage to assess the pre-test probability of sleep apnea. Those at high risk undergo a second stage, with an overnight evaluation at home with pulse oximetry or PM. Patients with a high pre-test probability of OSA but a negative test on PM may require further investigation by polysomnography, as the high positive predictive value but lower negative predictive value of PM means that while a positive test with PM is often adequate to diagnose OSA, a negative test may be inadequate in ruling out OSA [119].

Patients with evidence of frequent sleep-related oxyhaemoglobin desaturations or recurrent abnormal breathing episodes on PM should be referred, if possible, to a sleep specialist. In the absence of such clinical expertise, an empirical trial of CPAP therapy with an auto-titrating device can be considered with involvement of a primary care physician and a trained respiratory therapist. Undoubtedly, further research is needed given the countless barriers in identifying undiagnosed patients with OSA. Until formal evaluations of diagnostic strategies are available, a detailed history or a structured assessment followed by a simple nighttime evaluation will streamline those in urgent need for treatment.

## 7. Conclusions

There is a high prevalence of OSA in people with type 2 diabetes and abnormal glucose metabolism, which may in part be explained by obesity. Conversely, people with OSA have a high prevalence of type 2 diabetes and related metabolic disorders. There is a link between OSA and daytime

somnolence, hypertension and CVD. In a group already at high risk of CVD, consideration should be given to a contribution from OSA. Questionnaires and clinical characteristics may identify people with an increased likelihood of having OSA, and diagnosis can be confirmed by appropriate investigation. These studies have traditionally been conducted in an inpatient setting. However, where such facilities are limited, simpler home monitoring devices can aid in the diagnosis. Available therapies for OSA include weight reduction in the overweight and obese, reduction in alcohol intake, use of CPAP and use of dental appliances.

The benefits of treatment of OSA have been established for improvement in quality of life measures (e.g. improved sleep, reduced fatigue and daytime somnolence) and improved blood pressure control. Beneficial effects on glucose control, obesity and other cardiovascular risk factors have been suggested but have yet to be consistently demonstrated.

## 8.    Recommendations

The IDF calls for immediate action to be taken among the diabetes community to address the areas of awareness, clinical practice and research with respect to OSA and type 2 diabetes.

1. Awareness

All health professionals involved with diabetes or OSA should be educated about the links between the two conditions. Health policy makers and the general public must also be made more aware of OSA and the significant financial and disability burden that it places on both individuals and societies.

2. Clinical practice

Health professionals working in both type 2 diabetes and OSA should adopt clinical practices to ensure that a patient presenting with one condition is considered for the other. Health professionals should aim to develop locally appropriate clinical pathways for both type 2 diabetes and sleep services.

*Sleep services*: OSA patients should be routinely screened for markers of metabolic disturbance and cardiovascular risk. Minimum testing should include measurement of:

- waist circumference;
- blood pressure;
- fasting lipids;
- fasting glucose.

*Diabetes services*: The possibility of OSA should be considered in the assessment of all patients with type 2 diabetes and the metabolic syndrome.

- Patients should be assessed for symptoms of OSA: snoring, observed apnoea during sleep and daytime somnolence.
- There should be a low threshold for referral to establish the diagnosis, because of the established benefits of therapy on hypertension and quality of life.

- Management of OSA should focus initially on weight reduction for the overweight and obese. CPAP is the current best treatment for moderate to severe OSA and should be considered where appropriate.

3. Research

The IDF recommends research in the following areas:

- Epidemiological studies of prevalence of OSA in
  - patients with type 2 diabetes and metabolic syndrome;
  - children with obesity, especially those with type 2 diabetes;
  - different ethnic groups;
  - gestational diabetes and pre-eclampsia.
- Studies of the effects of OSA on
  - insulin secretion, insulin resistance, mitochondrial function and inflammatory markers;
  - complications of type 2 diabetes.
- Intervention studies
  - Appropriately powered randomised controlled trials of CPAP and other therapies in people with type 2 diabetes with emphasis on cardiovascular risk factors and outcomes, and glycaemic control. Additional outcomes should also include oxidative stress, inflammatory markers and adipokines/lipid metabolism.
  - Trials of weight loss in patients with OSA and diabetes (including use of anti-obesity medication).
- Resource development
  - A reliable but inexpensive diagnostic strategy for OSA to be used in a primary care setting.
  - Treatments for OSA that are easier to use and cheaper than CPAP.

## Conflicts of interest

## Acknowledgements

## Appendix A.  Working Group members

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