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Anne-Laure Borel, Renaud Tamisier, Philip Böhme, Pascaline Priou, Antoine Avignon, Pierre-Yves Benhamou, Hélène Hanaire, Jean-Louis Pépin, Laurence Kessler, Paul Valensi, et al.

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A.-L. Borel [a,b,*], R. Tamisier [b,c], P. Böhme [d,e], P. Priou [f,g], A. Avignon [h,i], P.-Y. Benhamou [a], H. Hanaire [j], J.-L. Pépin [b,c], L. Kessler [k], P. Valensi [l], P. Darmon [m], F. Gagnadoux [f,g]

[a] *Grenoble Alpes university hospital, endocrinology, diabetology, nutrition department, 38000 Grenoble, France*
[b] *Grenoble Alpes university, hypoxia pathophysiology laboratory, Inserm U1042, 38000 Grenoble, France*
[c] *Grenoble Alpes university hospital, thorax and vessels centre, physiology, sleep and exercise clinic, 38000 Grenoble, France*
[d] *University hospital of Nancy, endocrinology, diabetology, nutrition department, 54000 Nancy, France*
[e] *Lorraine university, EA4360 APEMAC, 54000 Nancy, France*
[f] *Angers university hospital, department of respiratory diseases, 49000 Angers, France*
[g] *Angers university, Inserm UMR 1063, 49000 Angers, France*
[h] *PhyMedExp, Montpellier university, Inserm, CNRS, 34000 Montpellier, France*
[i] *Montpellier university hospital, nutrition department, 34000 Montpellier, France*
[j] *Toulouse university hospital, Toulouse university, 31000 Toulouse, France*
[k] *University hospital of Strasbourg, diabetology department, Inserm UMR 1260, 67000 Strasbourg, France*
[l] *Department of endocrinology, diabetology, nutrition, AP–HP, Jean-Verdier hospital, Paris Nord university, CRNH-IdF, CINFO, 93140 Bondy, France*
[m] *Aix–Marseille university, endocrinology department, Inserm, Inra, C2VN, 13000 Marseille, France*

*Keywords:*
Continuous positive airway pressure
Obstructive sleep apnoea syndrome
Screening
Treatment
Type 1 diabetes
Type 2 diabetes

A B S T R A C T

*Aim.* – Because type 2 diabetes (T2D) is related to obesity, it is often associated with obstructive sleep apnoea syndrome (OSAS), although OSAS is also frequently diagnosed in patients with type 1 diabetes (T1D) and may promote gestational diabetes. Thus, this systematic review of the scientific evidence aimed to evaluate the epidemiological association between OSAS and all forms of diabetes, the current understanding of the pathophysiological mechanisms behind these associations, the expected benefits and limitations of OSAS treatment in patients with diabetes and, finally, to propose which patients require screening for OSAS.
*Methods.* – A panel comprising French expert endocrinologists and pneumologists was convened. Two of these experts made a search of the relevant literature for each subpart of the present report; all panel experts then critically reviewed the entire report separately as well as collectively.
*Results.* – There is little evidence to support the notion that OSAS treatment improves glycated haemoglobin, although it may improve nighttime blood glucose control and insulin sensitivity. However, there is robust evidence that OSAS treatment lowers 24-h blood pressure.
*Conclusion.* – The high prevalence of OSAS in patients with T1D and T2D justifies screening for the syndrome, which should be based on clinical symptoms, as the benefits of OSAS treatment are mainly improvement of symptoms related to sleep apnoea. There are also several clinical situations wherein screening for OSAS seems justified in patients with diabetes even when they have no symptoms, particularly to optimalize control of blood pressure in cases of resistant hypertension and microvascular complications.

## Introduction

Obstructive sleep apnoea syndrome (OSAS) and hypopnea are caused by complete or partial pharyngeal collapses repeatedly during sleep. These repeated collapses have four main consequences: desaturation–reoxygenation sequences; transitory episodes of hypercapnia; increased respiratory effort; and microawakenings that end the respiratory event. This is different from the central sleep apnoea that arises, for example, in cases of heart failure and causes respiratory pauses during sleep due to instability of the respiratory command and, thus, no increases in respiratory effort. Anomalies that reduce the diameter of the upper airways, such as retrognathism and micrognathism, can also lead

* Corresponding author at: CHU Grenoble Alpes, endocrinologie, diabète et maladies de la nutrition, CS10217, 38043 Grenoble cedex 9, France.
*E-mail address:* alborel@chu-grenoble.fr (A.-L. Borel).

to OSAS. In addition, OSAS can be induced by excess weight, which can reduce thoracic volume and the calibre of the upper airways [1].

OSAS is defined as the presence of apnoea (10-s interruptions of airflow), whereas hypopnoea refers to a decrease in respiratory flow of $\geq$ 30% in association with oxygen desaturation of $>$ 3% and/or microarousals. The condition is considered mild if the Apnoea–Hypopnoea Index (AHI; sum of apnoea plus hypopnea) is 5–14.9 events/h, moderate if 15–29.9 events/h and severe if $>$ 30 events/h. OSAS induces clinical signs including diurnal sleepiness, severe and daily snoring, sensation of choking or suffocating during sleep, daily fatigue, nycturia and morning headaches.

Because type 2 diabetes (T2D) is related to obesity, particularly abdominal obesity, it is often associated with OSAS. However, it appears that the association between OSAS and diabetes is not simply due to this shared aetiological factor, as OSAS is frequently diagnosed in those with type 1 diabetes (T1D) and can also promote gestational diabetes.

The present report summarizes the scientific evidence regarding the epidemiological association between OSAS and all forms of diabetes, and reviews our current understanding of the pathophysiological mechanisms behind these associations. In addition, the expected benefits from the treatment of OSAS in patients with diabetes and its limitations are also discussed and, finally, a strategy to identify patients who require screening is proposed.

To achieve these objectives, a panel of French expert endocrinologists and pneumologists was convened by the Société francophone du diabète (SFD; French-Speaking Society of Diabetes), Société de pneumologie de langue française (SPLF; French-Speaking Society of Pneumology) and Société française de recherche et médecine du sommeil (SFRMS; French Society of Sleep Research and Medicine). Two experts separately searched through the relevant literature on each subpart of the present report. All panel experts then critically reviewed the entire report on their own and as a group during face-to-face meetings.

## Epidemiology

### *Prevalence of OSAS in the general population*

OSAS prevalence was initially evaluated by three American cohort studies in the 1980s: the Wisconsin Sleep Cohort Study (WSC); the Sleep Heart Health Study (SHHS); and the Penn State Cohort (PSC). These studies found that male gender, increased age and obesity were factors associated with OSAS. However, as the prevalence of obesity has increased considerably since that time, the reported frequency of OSAS in those studies could no longer be directly extrapolated to today's population and, therefore, data on the prevalence of OSAS in the US from the WSC study have been re-estimated, using more recent population figures for the distribution of body mass index (BMI) scores, as measured between 2007 and 2010 by the third National Health and Nutrition Examination Survey (NHANES III). The initial screening was carried out using polysomnography in a population of American workers aged 30–70 years. The prevalence of moderate-to-severe OSAS, defined as an AHI score $>$ 15 events/h with daytime sleepiness [Epworth Sleepiness Scale (ESS) score $>$ 10], was 5.8% for men and 1.9% for women [2].

In Europe, the recent cohort study dubbed 'HypnoLaus' evaluated the prevalence of OSAS in the general Swiss population. In this work, 48% of participants were male, median age was 57 years and mean BMI was 25.6 kg/m$^2$. The prevalence of moderate-to-severe OSAS among those aged $<$ 60 years was around 7% for men and 2% for women [3].

### *Prevalence of OSAS in patients with diabetes*

Several studies have used nocturnal recordings to assess AHI in patients with diabetes (Table 1). In those with T2D, 58–86% of patients presented with an AHI $\geq$ 5 events/h, depending on the population studied, while 18–53.1% had an AHI $\geq$ 15 events/h. In patients with T1D, 10.3–40% had an AHI $\geq$ 15 events/h (Table 1), whereas a recent meta-analysis reported a mean prevalence of 16.7% of T1D patients with an AHI $\geq$ 15 events/h [4].

### *Prevalence of diabetes in patients with OSAS*

In 2014, the multinational European Sleep Apnoea Database (ESADA) cohort study [5], involving 24 sleep laboratories and 6616 adults, found a 6.6% prevalence of T2D in subjects without OSAS, and 14.1%, 21.0% and 28.9% in those with mild, moderate and severe OSAS, respectively. After adjusting for ethnicity, age, gender, sleep duration, smoking, alcohol consumption, ESS score, comorbidities, drug medication use, BMI and neck circumference, the odds ratios (ORs) for the presence of diabetes (known, treated, diagnosed by $HbA_{1c} > 6.5\%$) were 1.33 [95% confidence interval (CI): 1.04–1.72], 1.73 (95% CI: 1.33–2.25) and 1.87 (95% CI: 1.45–2.42) for mild, moderate and severe OSAS, respectively.

### *Incidence of diabetes in patients with OSAS*

A recent meta-analysis published in 2016 [6] combined the results of eight studies analyzing the relative risk (RR) of incident diabetes in patients with *vs* without OSAS. The presence of diabetes was confirmed by medical records and blood tests or reported by the participants themselves, although the type of diabetes was not always included. OSAS was diagnosed using different methods, depending on the study, such as AHI $>$ 5, AHI $>$ 8, 3% oxygen desaturation index $>$ 5, 4% oxygen desaturation index $>$ 30 and respiratory disturbance index (RDI) $>$ 5 events/h (corresponding to AHI plus microarousals related to respiratory events) or, again, reported by the patients themselves.

This meta-analysis revealed a significant risk of incident diabetes with moderate heterogeneity between studies ($I^2$: 47.9%) and an RR of 2.02 (95% CI: 1.57–2.61). Adjusting for age, gender and BMI reduced the RR to 1.49 (95% CI: 1.27–1.75) for all eight studies, and to 1.42 (95% CI: 1.02–1.99) for the two studies that used the criterion of an AHI $>$ 5 events/h.

## Carbohydrate metabolism disorders in patients with OSAS

Cross-sectional European [7], Asian [8] and US [9] studies involving large samples revealed the dose effects of severity of OSAS (AHI) and nocturnal hypoxaemia [minimum nocturnal pulse oxygen saturation ($SpO_2$)] on decreases of insulin sensitivity. These results were significant in both obese and non-obese patients after adjusting for confounding factors, such as age, neck circumference, alcohol intake and BMI. In a study of 118 patients without diabetes who underwent polysomnography, Punjabi et al. [10] also found dose effects of the severity of OSAS on decreases of insulin sensitivity and alterations of pancreatic beta-cell function (as measured by Bergman's minimal model) independently of age, gender and percentage of body fat (absorptiometry). Polotsky et al. [11] evaluated a population of patients with obesity and found similar results. Although these cross-sectional studies were controlled for several markers of body composition, visceral adiposity consistently remained an important confounding factor in analyses of the relationship between OSAS and carbohydrate metabolism disorders. Since then, two studies in thin subjects have shown that OSAS is also significantly associated with insulin

**Table 1**
Prevalence of nocturnal respiratory disturbances in patients with type 2 (T2D) and type 1 (T1D) diabetes.

| Authors | Population | *n* | Diagnostic methods | Mean BMI (kg/m$^2$) | Independent factors associated with increased AHI[a] | Prevalence of AHI > 15 events/h | Prevalence of AHI > 30 events/h |
|---|---|---|---|---|---|---|---|
| T2D | | | | | | | |
| Foster et al., 2009 [126] | Sleep AHEAD, multicentre, US, overweight/obese M (40%), F (60%) | 306 | PSG | 36.1 (5.6) for M 36.7 (5.9) for F | WC | 53.1% | 22.6% |
| Resnick et al., 2003 [127] | Sleep Heart Health Study, multiethnic, multicentre, F (54%), M (46%) | 470 | PSG | 31.3 (6.0) | NR | 23.8% | NR |
| Schöber et al., 2011 [128] | 14 primary-care centres, Germany, M (52%), F (48%) | 498 | Oximetry + oronasal airflow | 32.6 (6.7) | NR | 37.4% | NR |
| West et al., 2006 [129] | Single-centre, England, M (100%) | 240 | Oximetry, if > 10 events/h, → PG | 28.8 (4.9) | NR | 18% | NR |
| Einhorn et al., 2007 [72] | Single-centre, US, M (52%), F (48%) | 279 | ApneaLink™ | 33.5 (7.6) | Age > 62 years, BMI > 30 kg/m$^2$ if M | 36% (49% M, 21% F) | NR |
| Zhang et al., 2016 [130] | Multicentre, 12 hospitals, China | 880 | ApneaLink® | | BMI, WC | 25.6% | 10.3% |
| Vale et al., 2013 [131] | Single-centre, Portugal | 23 | PG | 29.2 (3.8) | NR | 34.8% | NR |
| Laaban et al., 2009 [70] | Single-centre, France, diabetic, hospitalized | 303 | PG | NR | BMI, WC, NC | 19% | 10% |
| T1D | | | | | | | |
| Schöber et al., 2011 [128] | 14 primary-care centres, Germany, M (53%), F (47%) | 58 | ApneaLink® | 25.4 (5.1) | NR | 10.3% | NR |
| Vale et al., 2013 [131] | Single-centre, Portugal | 23 | PG | 28.0 (5.1) | NR | 26.1% | NR |
| Manin et al., 2015 [79] | Single-centre, M (60%), F (40%), France | 67 | PSG | 25.8 (4.7) | Diabetes duration, DR, DN, CVD, HTN | 38% | 19% |
| Borel et al., 2010 [132] | Single-centre, France, M (68%), F (32%) | 37 | Oximetry, then PSG if pathological | 24.7 (3.0) | NR | NR | 40% |
| Reutrakul et al., 2016 [4] | Meta-analysis (4 studies), France, Germany, Brazil | 186 | | | NR | 16.7% | |

AHI: apnoea–hypopnoea index; BMI: body mass index; M: male; F: female; PSG: polysomnography; WC: waist circumference; NR: not reported; PG: polygraphy (ventilatory); NC: neck circumference; DR: diabetic retinopathy; DN: diabetic neuropathy; CVD: cardiovascular disease; HTN: hypertension.
[a] Independent factors associated with AHI in multivariate models. The dependent variable could be AHI as a continuous variable or AHI above 15 events/hour depending on the study.

resistance in such subjects too [12,13]. Thus, it appears that OSAS is associated with loss of insulin sensitivity, and this association is independent of the confounding presence of excess adipose tissue (particularly visceral) in these patients.

Several studies have shown that changes in carbohydrate metabolism are more strongly associated with indices of nocturnal hypoxaemia (mean $SpO_2$, time spent at < 90% $SpO_2$) than with the AHI [8,14–17]. Respiratory events arising specifically during paradoxical sleep also appear to have a major impact on carbohydrate control [16].

In addition, two large-scale cross-sectional cohort studies in subjects who had undergone screening for OSAS found an increased risk of prediabetes (defined as $HbA_{1c}$ values 6–6.49%) in patients with OSAS (OR: > 2) [5,15], with dose effects related to AHI scores and time spent at < 90% $SpO_2$ [15]. These results are summarized in Table 2, which does not include all related studies, but is nonetheless representative of the current evidence.

## Pathophysiological mechanisms associated with OSAS

### *Immediate consequences: sleep fragmentation, intermittent hypoxia, changes in intrathoracic pressure*

The immediate consequences of respiratory events during sleep are intermittent hypoxia (sequential desaturation–reoxygenation cycles), transient increases in various 'capnias' during pharyngeal collapse, considerable variations in intrathoracic pressure (resulting from patients' respiratory efforts to fight collapses), and microarousals terminating the respiratory event and leading to fragmented sleep. Among these stimuli, severity of intermittent

**Table 2**
Representative studies of carbohydrate metabolism in patients with obstructive sleep apnoea syndrome (OSAS) but no diabetes.

| Authors | Population (*n*) | Study design | Measurement method | Results |
|---|---|---|---|---|
| Meslier et al., 2003 [133] | 578 | Prospective, cross-sectional | GTT | Association between AHI severity and changes in insulin sensitivity |
| Punjabi et al., 2004 [9] | 2656 | Prospective cross-sectional | GTT, HOMA-IR | Glucose intolerance if AHI > 15 (OR: 1.46); HOMA-IR higher if AHI > 15 or more severe nocturnal hypoxaemia |
| Theorell-Haglow et al., 2008 [7] | 400 women | Prospective cross-sectional | Insulin sensitivity index/GTT | Association between severity of AHI or $SpO_2$ min and decreased insulin sensitivity |
| Ip et al., 2002 [8] | 270 | Prospective cross-sectional | Fasting glycaemia, HOMA-IR | OSAS (AHI and $SpO_2$ min) associated with insulin resistance in obese and non-obese |
| Priou et al., 2012 [15] | 1599 | Prospective cross-sectional | Prediabetes ($HbA_{1c}$: 6–6.49%) | Increase in risk of prediabetes if OSAS severe (AHI, time at < 90% saturation) |
| Kent et al., 2014 [5] | 5294 | Prospective cross-sectional | $HbA_{1c}$, prediabetes | Association between AHI and $HbA_{1c}$; increased risk of diabetes in last quartile of AHI (OR: 2.12) |

GTT: glucose tolerance test; AHI: Apnoea–Hypopnoea Index; HOMA-IR: homoeostasis model assessment for insulin resistance; OR: odds ratio; $SpO_2$: pulse oxygen saturation; $HbA_{1c}$: glycated haemoglobin.

nocturnal hypoxaemia is the main determining factor and predictor of cardiovascular and metabolic complications.

*Intermediate mechanisms: change in sympathovagal balance, oxidative stress, low-grade inflammation, hormonal changes, metabolic flow*

Repeated intermittent hypoxic respiratory events lead to the development of chronic adaptive mechanisms. Studies in both animals and humans have shown that exposure to intermittent hypoxia leads to sympathetic hyperactivity [18,19], systemic and vascular inflammation via nuclear factor-kappa light-chain enhancer of activated B cells (NF-κB) [20–23], oxidative stress [24] and proinflammatory stimulation of adipose tissue via hypoxia and hypoxia-inducible factor (HIF)-1 [adiponectin reduction and macrophage infiltration via increased monocyte chemoattractant protein 1 (MCP1)] [25,26]. Sleep fragmentation also disrupts the nychthemeral cycle of cortisol secretion and somatotropic axis, leading to a decrease in insulin-like growth factor (IGF)-1 [27–30].

*Consequences of intermediate mechanisms*

*Endothelial dysfunction, changes in blood pressure, arterial rigidity*

Sympathetic hyperactivity, inflammation and oxidative stress result in endothelial dysfunction and vascular remodelling, characterized by increased arterial rigidity and atherosclerosis [31,32]. Endothelial dysfunction leads to a reduction in nitric oxide (NO) production, thereby reducing vasodilatation in response to increased vascular flow (shear stress), while increasing vasoconstriction. Intermittent hypoxia also activates sympathetic hyperactivity and the renin–angiotensin–aldosterone system (RAAS), two mechanisms that reinforce vasoconstrictor tone with no arterial baroreflex counterregulation as baroreflex sensitivity is reduced by intermittent hypoxia. These mechanisms account for the dose–response relationship between OSAS and arterial hypertension.

Endothelial dysfunction and the subsequently modified microcirculation may also contribute to the microvascular complications of diabetes by promoting an increase in advanced products of glycation and changes in protein kinase C signalling [33,34]. As regards renal function, arterial hypertension and abnormalities in RAAS regulation might explain the link between OSAS and diabetic renal disease [35].

*Insulin resistance, insulin secretion and dyslipidaemia*

Sympathetic hyperactivity increases glycogenolysis and hepatic gluconeogenesis. The flow of free fatty acids to the liver and muscles is also increased by activation of lipolysis, which promotes insulin resistance as well as aggravates non-alcoholic fatty liver disease [36]. In addition, laboratory studies have shown that intermittent hypoxia induces apoptotic oxidative stress-related effects on pancreatic beta-cells [37,38] and adipose tissue inflammation while also promoting lipolysis [39]. OSAS severity is dose-dependently related to combined dyslipidaemia [raised triglyceride levels with decreases in high-density lipoprotein (HDL) cholesterol] after adjusting for confounding factors [40].

Furthermore, the microarousals characteristic of OSAS affect various phases of sleep: there are fewer and/or shorter phases of deep sleep, for example. Tasali et al. [41] carried out a study where they specifically prevented the slow-wave deep sleep phase for three consecutive nights in nine young adults with no risk factors for diabetes. However, these sleep perturbations caused an increase in body weight and reduced insulin sensitivity. Thus, in addition to the mechanisms shared with intermittent hypoxia, sleep fragmentation may also increase food consumption (specifically through increased hunger and reduced satiety) via decreases in leptin and increases in ghrelin production [42] (Fig. 1).

## Risks related to OSAS

*Effects on quality of life and greater risk of accidents*

Daytime sleepiness due to sleep fragmentation through repeated micro-awakenings is the main measure related to poorer quality of life. Such sleepiness is considered severe if it significantly disrupts a person's social and professional life, and affects everyday activities such as eating, driving and spending time with family. In addition, daytime loss of vigilance can lead to dangerous situations due to the possibility of falling asleep while driving or at work [43,44], and may also lead to cognitive disorders (affecting attention, memory, concentration) [45]. For patients with diabetes and OSAS, the risk of traffic accidents is exacerbated by iatrogenic hypoglycaemia. However, continuous positive airway pressure (CPAP) treatment has been demonstrated to be an effective measure for alleviating daytime sleepiness [46–48].

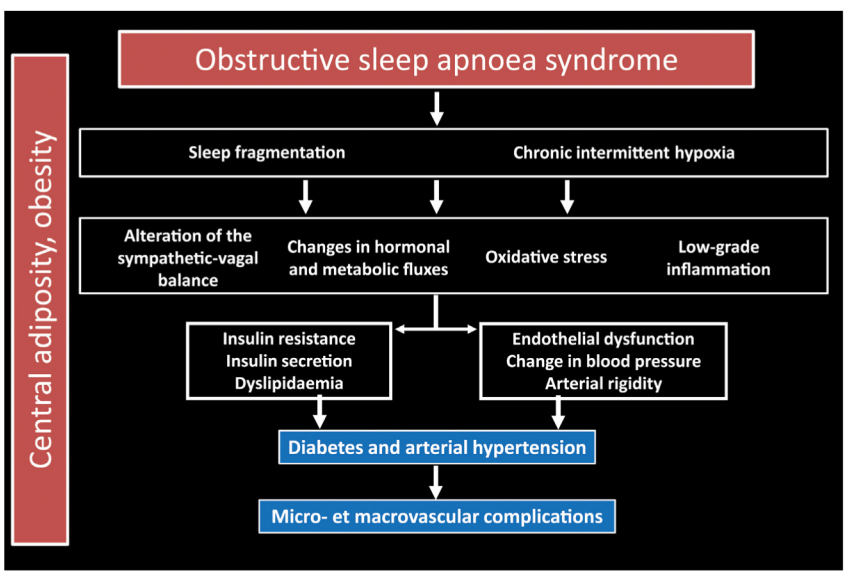


**Fig. 1.** Summary of the metabolic effects of obstructive sleep apnoea syndrome (OSAS).

*Effects of OSAS on arterial hypertension*

OSAS modifies the nycthemeral cycle of arterial pressure: patients lose the normal nocturnal 10–20% reduction in arterial pressure in comparison to daytime pressure, thereby defining the so-called 'non-dipper' or even 'reverse-dipper' blood pressure profile [49–51]. Such changes in people with OSAS, whether they have arterial hypertension or not, have been associated with increased cardiovascular events and stroke [52,53]. In fact, the prevalence of hypertension has been shown to increase with severity of OSAS [54–56]. Results suggest that both moderate and severe OSAS (AHI $>$ 15 events/h) are associated with higher risks of developing hypertension [54,57], particularly in men aged $<$ 60 years if sleepiness is present. OSAS affects 83% of patients with resistant arterial hypertension, defined as uncontrolled arterial pressure despite improvements in diet and exercise and the administration of triple therapy (including optimal doses of thiazide diuretics).

Indeed, there appears to be a strong relationship between OSAS and hypertension, a fact that most likely explains the reported relationship between OSAS and cardiovascular morbidity and mortality, especially stroke [58] and left ventricular hypertrophy (LVH) [59,60].

*Effects of OSAS on cardiovascular disorders*

The impact of OSAS on the risk of cardiovascular disease depends on symptoms, number of nocturnal desaturations and, in particular, presence of cardiometabolic comorbidities that are themselves important prognostic factors in OSAS [61–63]. Several cohort studies have indicated that OSAS is itself associated with increases in mortality and incidence of cardiovascular events [61,64,65]. In addition, the multinational Sleep and Stent Study, which included mostly Asian patients, found that OSAS was related to an increase in the RR of fatal and non-fatal cardiovascular events after coronary revascularization. A posteriori analyses showed significant interactions with the presence of diabetes, and the excess risk related to OSAS was significant in patients with diabetes (adjusted RR: 2.03, 95% CI: 1.10–3.74) compared with those without diabetes (adjusted RR: 1.12, 95% CI: 0.57–2.17), after adjusting for age, gender, ethnic origin and hypertension [66].

*Effects of OSAS on blood glucose levels*

Several studies found positive correlations between severity of OSAS and increased $HbA_{1c}$ in patients with diabetes (mostly T2D), even after adjusting for the main confounding factors and the use of several outcome measures [5,16,67–69]. The European ESADA cohort study [5] found that patients with diabetes and severe OSAS were at greater risk of poorly controlled diabetes ($HbA_{1c}$ $>$ 7%) compared with those without OSAS (OR: 2.02, 95% CI: 1.11–3.66; $P$ = 0.022 for tendency). Data were adjusted for centre, age, gender, ethnic origin, smoking, alcohol intake, daytime sleepiness, BMI, neck circumference, comorbidities and glucose-lowering therapies. A positive relationship was also found between OSAS severity and evidence of poor blood glucose control, with mean adjusted levels of $HbA_{1c}$ of 6.76%, 6.70%, 6.88% and 7.48% in diabetes patients with no, mild, moderate and severe OSAS, respectively. As for sleep architecture, respiratory events during paradoxical sleep may have the greatest negative impact on glucose control [16]. In contrast, several other studies (albeit with smaller cohort samples) failed to find any such relationship [70–72].

Overall, OSAS severity and altered blood glucose control appear to be correlated in patients with T2D. In addition, compared with having no or moderate OSAS, severe OSAS has been associated with $HbA_{1c}$ increases of 0.5–0.8% (after adjustment), depending on the study sample size and methodological biases [73].

*Effects of OSAS on diabetes-related microvascular complications: retinopathy, nephropathy, neuropathy*

A meta-analysis of seven studies of patients with T2D found that OSAS was associated with an increased risk of a reduced glomerular filtration rate (GFR) to $<$ 60 mL/min (OR: 1.59, 95% CI: 1.16–2.18) [74]. In one cross-sectional study, hypoxaemia severity was associated with severity of diabetic renal disease according to stage of microalbuminuria [75], while another study of 196 patients with T2D, followed for 2.5 years, found that GFR decreased more rapidly in patients with than without OSAS. In fact, this association remained independent in a multivariate regression model that included initial GFR, diabetes duration, ethnic origin, BMI, gender, mean arterial pressure, antihypertensive medication, oral antidiabetic medication and insulin, lipid-lowering treatment, antiplatelet aggregation medication, total cholesterol and triglycerides, $HbA_{1c}$ and smoking [76].

One study found OSAS to be a predictive factor for preproliferative retinopathy (168 patients analyzed) after adjusting for ethnic origin, gender, diabetes duration, age at time of diabetes diagnosis, mean arterial pressure, $HbA_{1c}$, BMI, GFR, oral antidiabetic medication and insulin, and antihypertensive medication. However, OSAS did not appear to influence the progression of maculopathy in that cohort (199 patients analyzed) [77].

A meta-analysis pooling 868 patients with T2D from five cross-sectional studies compared the presence of OSAS in those with diabetic neuropathy (DN; whether autonomic or sensory) vs. without DN; the results were not significant (OR: 1.90, 95% CI: 0.97–3.71; $P$ = 0.06) [78]. There are fewer data available for patients with T1D: one cross-sectional study of 67 patients found that autonomic neuropathy (assessed from clinical symptoms) was significantly more prevalent in patients with vs. without OSAS (37% vs. 21%, respectively) [79].

These data all suggest that OSAS might play a role in microangiopathic complications or their progression in patients with T2D, although this needs to be confirmed by further studies.

*Effects of OSAS on gestational diabetes*

Pregnancy causes physiological and hormonal changes as well as changes in sleep architecture that can either promote OSAS development or worsen preexisting OSAS. Gestational weight gain and a raised diaphragm can predispose to OSAS, while upper airways congestion due to hypervolaemia and the effects of oestrogens can also contribute to OSAS [80].

Pregnancy is normally associated with a certain degree of insulin resistance and so may constitute a period of particular vulnerability to the negative effects of OSAS [81]. Indeed, the relationship between OSAS and gestational diabetes was evaluated by recent meta-analyses pooling observational studies involving several thousands of participants: the result was a gestational diabetes RR of between 2 and 3, which persisted after adjusting for obesity, although it did appear to be higher in obese women [82–84].

These studies, however, have several limitations, including the fact that OSAS was diagnosed based on the presence of snoring or data from questionnaires, and only occasionally by polysomnography. Recently, the Nulliparous Pregnancy Outcomes Study, a multicentre cohort of nulliparous pregnant women, assessed the prevalence of sleep breathing disorders during pregnancy ($n$ = 3306), and its association with preeclampsia, hypertensive disorder and gestational diabetes [85]. Nocturnal respiratory polygraphy was performed twice, first between 6 and 15 weeks of pregnancy, and then again between 22 and 31 weeks. The prevalence of AHI $\geq$ 5 events/h was 3.6% in early pregnancy and 8.3% in mid-pregnancy. On logistic regressions adjusted for

maternal age, BMI, chronic hypertension and, for mid-pregnancy, rate of weight gain/week between early and mid-pregnancy assessments, a significant association was found between AHI $\geq$ 5 events/h and preeclampsia (OR: 1.94, 95% CI: 1.07–3.51 in early pregnancy; OR: 1.95, 95% CI: 1.18–3.23 mid-pregnancy), gestational diabetes in early and mid-pregnancy (OR: 3.47, 95% CI: 1.95–6.19 and OR: 2.79, 95% CI: 1.63–4.77, respectively), and hypertension (mid-pregnancy only; OR: 1.73, 95% CI: 1.19–2.52).

These results were confirmed in a recent meta-analysis that also found no association with adverse fetal maternal outcomes (APGAR score, birth weight) [86]. In one study of women with diet-controlled gestational diabetes, the degree of oxygen desaturation correlated with fasting glucose, insulin resistance and beta-cell function [87]. In a small sample of 25 patients with gestational diabetes, an AHI $\geq$ 5 events/h (seen in 17%) was associated with blunted cortisol awakening responses, but with preserved circadian variation of cortisol [88].

## Expected treatment effects

CPAP is the main treatment for moderate-to-severe OSAS. Applied to the upper airways through a nasal or oronasal mask, CPAP provides a pneumatic splint to prevent pharyngeal collapse [89]. The mask must be used for at least 4 h/night to achieve its therapeutic goals. However, only around 60% of patients treated with CPAP are sufficiently compliant to render the treatment effective [90]. CPAP is especially suitable for patients with severe OSAS (AHI $\geq$ 30 events/h).

Mandibular advancement devices (MADs) are the main alternative to CPAP. Two moulded dental-arch guards are linked together to advance the mandible by variable degrees to increase the pharyngeal space and limit its collapse. However, the feasibility and effectiveness of these devices have never been specifically evaluated in patients with diabetes, whereas MADs therapy is contraindicated in people with severe periodontal disease, a frequent finding in diabetes patients. MADs are also less effective than CPAP for reducing AHI scores (mean AHI reduction $\approx$ 60% vs. $\approx$ 84% with CPAP), and have considerable interindividual variability. Moreover, there are no robust data to determine the effect of MADs on risk of accidents and cardiometabolic comorbidities associated with OSAS.

### *Impact on clinical symptoms*

The beneficial effects of CPAP on daytime sleepiness and quality of life have been clearly demonstrated in patients with moderate-to-severe forms of OSAS [91]: regular CPAP treatment of these forms has, for example, been associated with a reduced risk of road traffic accidents [45,92]. The benefits of CPAP on sleepiness and quality of life have also been demonstrated in patients with diabetes [93–95]. One study of 182 such patients found a small (but significant) reduction in symptoms such as snoring, nycturia, sleepiness and poor sleep quality with *vs* without CPAP treatment [96].

Any benefits of CPAP are generally seen after several weeks, and patients should be able to then experience normal quality of life. In addition, after excluding other pathologies, only 6% of patients effectively treated with CPAP continue to have persistent sleepiness [97].

### *Impact on arterial hypertension*

Regular CPAP therapy for OSAS results in modest reductions of blood pressure [98]. A recent meta-analysis pooled the results of 24-h recordings from five randomized clinical trials, and found reductions in both systolic and diastolic blood pressure of -4.78 mmHg (95% CI: −7.95 to −1.61) and -2.95 mmHg (95% CI: −5.37 to −0.53), respectively, in patients with resistant hypertension treated with CPAP [99]. These results suggest that patients with OSAS and resistant hypertension have better blood pressure responses to CPAP. Likewise, randomized trials of patients with diabetes have also found lower blood pressure with CPAP [94].

### *Impact on cardiovascular risk*

An observational study with a 10.1-year follow-up revealed greater incidences of both fatal [myocardial infarction (MI) or stroke] and non-fatal (MI, stroke, bypass or coronary angioplasty) cardiovascular events in people with severe rather than mild-to-moderate OSAS, simple snorers, those treated with CPAP and healthy subjects [65]. These data suggest that CPAP does indeed have preventative effects.

In addition, four randomized trials have investigated the effects of CPAP on cardiovascular events in people with OSAS [100–103]. One was a multicentre study of 725 subjects with no history of cardiovascular disease [100], while another was a single-centre study of patients with coronary disease who had just undergone revascularization [101]. After several years of follow-up, neither study found any differences between CPAP patients and their controls regarding the composite cardiovascular endpoint, although the prognosis was better in those who were more compliant with treatment ($\geq$ 4 h/night) than those using CPAP for $<$ 4 h/night.

Similarly, a study of patients who had recently had a stroke found that CPAP treatment did not change their cardiovascular prognosis [102]. The Sleep Apnoea Cardiovascular Endpoints (SAVE) study was an international multicentre controlled trial of secondary prevention that included 2717 patients with moderate-to-severe OSAS and coronary or cerebrovascular disease, of whom 30% also had diabetes [103]. At the end of an average follow-up of 3.7 years, no significant effects of CPAP were found for either the composite endpoint of cardiovascular mortality, infarction, stroke, hospitalization for unstable angina and transient ischaemic attacks or for each criterion on its own.

A recent meta-analysis [104] of 10 randomized controlled trials (RCTs), involving 7266 patients with OSAS and comparing CPAP with either no treatment or sham CPAP, found no reduction of risks of either cardiovascular events or cardiovascular mortality. In addition, no significant interaction ($P$ = 0.09) was found in the subgroup analysis based on treatment compliance ($>$ or $<$ 4 h/night).

However, these randomized studies had important limitations: for example, the sample size planned for the SAVE study was never reached [105]. However, the main limitation was that the study included mostly patients with moderate OSAS, patients who typically have fewer symptoms and poorer compliance with treatment (around 3 h/night). Patients with more severe and symptomatic OSAS were excluded, as it was considered unethical to withhold treatment from such patients for several years. Thus, it is difficult to extrapolate these results to the entire patient population with OSAS.

### *Impact on blood glucose and prevention of diabetes-related microangiopathy*

The effects of treatment with CPAP on insulin sensitivity and glycaemic control remain controversial. The available data are discordant and often from poor-quality studies with short follow-up durations and small sample sizes.

#### *Insulin sensitivity*

Despite many negative observational studies, one meta-analysis of patients with diabetes that included 12 before-and-after studies found a significant effect of CPAP on insulin

sensitivity, as evaluated by homoeostasis model assessment for insulin resistance (HOMA-IR) [106]. A modest yet significant effect was also found in another meta-analysis that included five randomized trials of 244 patients without diabetes, and compared CPAP with placebo for between 6 weeks and 6 months [107–110]. In patients with T2D and OSAS, CPAP treatment for 12–16 weeks showed improvement in insulin sensitivity as measured by the glucose clamp technique [111,112]. These data suggest that CPAP can modestly improve insulin sensitivity.

*Blood glucose control*

In patients with T2D, observational studies have shown no significant decreases of $HbA_{1c}$ with CPAP except in subgroups with initially high $HbA_{1c}$ levels [113,114]. One study, based on a cohort of patients followed in general medicine in the UK, analyzed 150 patients with T2D and OSAS (treated with CPAP) and 150 matched patients who also had T2D but with untreated OSAS. Five years after diagnosis, patients treated with CPAP had lower blood pressure and markedly better $HbA_{1c}$ than those not treated with CPAP. Unfortunately, in this non-randomized trial, the reasons why control patients had not received CPAP were not reported. One possible explanation is that the untreated patients were less compliant with treatments in general in comparison to other groups of patients treated with CPAP [95]. Myhill et al. [115] randomized 55 well-controlled T2D patients (estimated sample size of 100) into immediate and delayed 3-month CPAP intervention groups and pooled both of them for analysis, making this study uncontrolled. There was no improvement in $HbA_{1c}$, which was initially at a median of 7.0% [interquartile range (IQR): 6.4–8.7%]. However, patients demonstrated significant drops in systolic and diastolic blood pressure and heart rate, which were associated with decreases in urinary levels of dopamine and noradrenaline.

To date, five RCTs measuring the effects of CPAP on glucose control in patients with T2D and OSAS have been published. In the study by West et al. [93], 42 men with T2D and moderate-to-severe OSAS were treated with active or inactive CPAP for 3 months. The results showed no differences in either $HbA_{1c}$ or insulin sensitivity as measured by clamp test. Shaw et al. [94] included 298 T2D patients (mean initial $HbA_{1c}$: 7.3%) in a randomized 6-month trial comparing CPAP with "usual treatment" and found no improvement in $HbA_{1c}$ with active CPAP, not even when analyses was carried out only with those who had the most uncontrolled diabetes, those with severe OSAS and those most compliant with the treatment. In contrast, in the study by Martinez-Ceron et al. [116], 50 T2D patients (mean $HbA_{1c}$: 7.6%) who randomly received either CPAP or "usual treatment" showed significantly greater improvement in $HbA_{1c}$ in the CPAP than in the control group ($HbA_{1c}$: -0.4%; $P < 0.03$). This randomization was intended to identify the potential role of lifestyle counselling as well as the role of CPAP. Lam et al. [117] included 60 patients in an RCT of CPAP vs. controls. Although CPAP failed to decrease $HbA_{1c}$ in the intention-to-treat analysis, it did improve blood pressure. On excluding patients who changed their body weight or antidiabetic medication from the analysis, CPAP intervention was associated with a -0.4% (−0.7 to −0.1) decrease in $HbA_{1c}$ ($P = 0.027$). Finally, Mokhlesi et al. [116] carried out a 'proof of concept' study with 22 T2D patients who were either untreated or using only oral treatment; these patients slept for 7 days in a sleep laboratory using active or inactive CPAP for 8 h/night. After 1 week, mean 24-h blood glucose levels were improved in the active vs. inactive CPAP treatment group. This improvement was striking in relation to nighttime glycaemic levels and even more marked in patients with the highest glycaemic levels at inclusion.

Three further studies evaluated interstitial glucose continuously throughout the night using Holter glucose monitoring. After > 1 month of CPAP, significant improvement in nighttime blood glucose levels and glycaemic variability was observed in two of the studies [118,119], but not in the third one, wherein only fructosamine levels decreased with CPAP compared with sham CPAP in 23 randomized patients [120].

The potential benefits of CPAP therapy were also recently tested in obese women with gestational diabetes and AHI ≥ 5 events/h. In this study, 36 women were randomized to receive either 2-week CPAP or control treatment. CPAP failed to improve glucose levels, but did improve insulin secretion when adherence to treatment was adequate (≥ 4 h/night for ≥ 70% of nights) [121].

Analyses of all these studies suggest there is little evidence to support CPAP-improved $HbA_{1c}$ levels in patients with T2D (except perhaps in those with initially high $HbA_{1c}$ levels). However, CPAP treatment can improve nighttime blood glucose control and blood pressure in patients with T2D, although the supportive evidence is weak according to the literature. Moreover, interventional studies have yet to be carried out in patients with T1D and OSAS.

*Diabetes-related microvascular complications*

Very few studies have evaluated the role of CPAP on diabetes-related microvascular complications. A cohort study ($n = 164$) by Altaf et al. [77] reported on a subset of 38 patients with moderate-to-severe OSAS, of whom 15 consented to treatment with CPAP. The findings suggested that pre-proliferative and proliferative retinopathy in the 15 treated with CPAP had slower disease progression than the remaining 23 not using CPAP. While these results are interesting, they nonetheless should be interpreted with caution, as the sample size was small and treatment allocation not randomized.

In a cohort study by Tahrani et al. [76] involving 47 patients with moderate-to-severe OSAS who were offered CPAP treatment, 16 accepted and 31 refused. However, no differences were found in progression of diabetic kidney disease between the two groups. Also, as with the above-mentioned study, it was not possible to draw definitive conclusions from this work as, again, the sample size was small and treatment allocation was non-randomized. Finally, no studies of the effects of CPAP on DN were found in the literature.

## Which patients should be screened?

The first step of screening for sleep-related respiratory disorders should be a patient interview. All patients should be routinely interviewed for clinical symptoms of OSAS, even when they have no other risk factors (central adiposity, male gender, age > 50 years). For patients with diabetes as well as the general population, the primary aim of treatment is to improve symptoms. Thus, our proposal is that clinicians should ask simple questions to detect symptoms of OSAS, such as the usual presence of snoring, witnessed apnoea, awakenings with feelings of suffocation, nycturia, headaches, daytime tiredness/sleepiness or feeling unrefreshed despite a night's sleep. In cases where symptoms are present, the expected symptomatic relief with CPAP justifies nighttime recordings to screen for disordered breathing during sleep. This suggestion is supported by both the high prevalence of OSAS in patients with T2D and the demonstrated ability of CPAP to improve OSAS-related symptoms.

In addition, there are several clinical situations independent of symptoms where improvement may be expected with OSAS treatment in patients with diabetes, even in the absence of any functional symptoms of the syndrome (Table 3). In particular, OSAS should be considered in patients with T1D because its prevalence is high in these cases and independent of BMI. Indeed, particular attention should be paid to patients with long-standing diabetes (> 20 years) and the presence of autonomic neuropathy [122]. However, as there are no studies of the benefits of OSAS

**Table 3**
Clinical situations indicating screening for obstructive sleep apnoea syndrome (OSAS) in patients with diabetes even when free of symptoms.

| Clinical situation | Justification for screening |
|---|---|
| Resistant hypertension[a] | Beneficial effects of CPAP on blood pressure (meta-analysis of randomized trials) |
| Rapidly progressing renal complications (GFR decreases by $>$ 5 mL/min/1.73 $m^2$ per annum) despite good medical treatment | Improved control of blood pressure over 24-h with CPAP might protect target organs (kidneys, eyes), despite no available studies |
| Retinal disease and complications | Improved control of blood pressure over 24 h with CPAP might protect target organs (kidneys, eyes), despite no available studies |
| High insulin resistance in type 2 diabetes | CPAP might improve insulin sensitivity (cohort studies, subgroups in randomized trials), despite no studies in this specific population |

CPAP: continuous positive airway pressure; GFR: glomerular filtration rate.
[a] Persistent hypertension despite lifestyle changes and administration of three antihypertensive drugs, including a thiazide diuretic.

treatment in this population, a treatment test to evaluate any clinical improvement seems justified.

In addition, as the risk of road traffic accidents is increased by OSAS and prevented with CPAP treatment, T2D patients whose professions involve driving should be screened for OSAS. It is clear that clinical attention should be focused on the risk of sleepiness and iatrogenic hypoglycaemia when these two pathologies are associated in such patients.

*Relevance of screening questionnaires for diabetes patients*

Clinical sleep screening questionnaires, such as the Berlin (BQ), STOP and STOP-Bang (SBQ), have been validated in the general population. The BQ seeks to identify symptoms of OSAS (snoring, nocturnal suffocation, fatigue, daytime sleepiness) and the presence of arterial hypertension. The STOP and SBQ include calculations of BMI and neck circumference. When these questionnaires were evaluated in T2D patients, however, they were found to have low sensitivity and specificity: at best, the BQ only had a sensitivity of 69% [123], whereas the low specificity of these questionnaires in such patients could be related to the fact that several questions refer to factors shared by OSAS and T2D, such as high BMI scores, increased neck circumference (indicative of central obesity) and arterial hypertension.

The ESS questionnaire evaluates subjective daytime sleepiness which, when excessive, is one of the principal symptoms of OSAS; even though it affects only 57% of patients [124], it is present in $>$ 10% of the general population [125]. In patients with cardiometabolic morbidities (refractory arterial hypertension, cardiac failure, the metabolic syndrome), excessive daytime sleepiness is unusual, resulting in a mean ESS score of $<$ 8 out of a possible 24 [103]. Sleepiness is therefore not sufficiently discriminatory to detect OSAS in these populations and, thus, the ESS questionnaire should not be used for OSAS screening. Moreover, in our opinion, the above-mentioned questionnaires are not relevant for patients with diabetes.

## Conclusion and future prospectives

The high prevalence of OSAS in patients with either T1D or T2D justifies screening for the syndrome, which should be based on clinical symptoms, as the benefits of CPAP treatment consist mainly of improvement of symptoms related to sleep apnoea. In addition, there are a few clinical situations in which screening for OSAS seems justified in patients with diabetes despite the absence of symptoms and, in particular, to optimalize control of blood pressure in cases of resistant hypertension and microvascular complications, but also when driving is part of the patient's job or profession. Our present review of literature has also highlighted gaps that should be considered pointers for future research.

The pathophysiological mechanisms of OSAS in the context of diabetes that lead to the greater prevalence of OSAS in T2D patients independently of obesity are as yet still unknown. Likewise, the mechanisms behind the high prevalence of OSAS in T1D patients who are not overweight are still not understood either. The hypothesis that neuropathy may have its own role in the pathophysiology of OSAS in patients with either T1D or T2D remains to be investigated.

Regarding OSAS screening of patients with diabetes, the role of nocturnal oximetry in the decision-making algorithm for either initiation of treatment (if oximetry is highly abnormal) or halting further investigations (if oximetry is normal) is as yet insufficiently documented. In addition, given the aim of bringing symptomatic relief, future studies should now assess whether clinical symptom-based questionnaires are relevant for identifying those diabetes patients who should undergo sleep recordings (as suggested in this review) rather than recording and treating all such patients independently of their symptoms.

In addition, the benefit–risk ratio of OSAS treatment by MADs has not been documented in diabetes patients, and the effects of CPAP treatment on nocturnal blood glucose levels and nocturnal hypoglycaemia are as yet inadequately established. Indeed, converting such changes of intermediary markers into 'hard' clinical events should also be investigated, as should also the effects of CPAP on blood glucose control in patients with T2D, who are characterized by marked insulin resistance. Moreover, the effects of CPAP on $HbA_{1c}$ in patients with T1D should now be evaluated, as should also the roles of OSAS and its treatment by CPAP in cases of non-alcoholic steatohepatitis in patients with diabetes.

**Funding**

This research received no specific grants from funding agencies in the public, commercial or not-for-profit sectors.

**Disclosure of interest**

ALB: declares having received honoraria, grants and other fundings from Agiràdom, NovoNordisk, MSD, GILEAD, Novartis.
PB: declares having received honoraria, grants and other fundings from Sanofi, Novartis, Novo Nordisk, Merck Sharp & Dohme, Roche Diagnostic, Dinno Santé.
AA: declares having received honoraria, grants and other fundings from Astra-Zénéca Lilly, Abbott, Novo-Nordisk, MSD.
PYB: declares having received honoraria, grants and other fundings from; HH declares having received support from Abbott, Eli Lilly, Lifescan, Novo Nordisk, Medtronic, Sanofi Aventis, Servier, Vitalaire.
JLP: declares having received honoraria, grants and other fundings from Air Liquide Foundation, Agiradom, AstraZeneca, Fisher and Paykel, Mutualia, Philips, Resmed, Vitalaire, Boehringer Ingelheim, Jazz pharmaceutical, Night Balance, Philips, Resmed, Sefam.
LK: declares having received funding from avec Elivie, Vitalair, IP-Santé, Abbott, Medtronic, Johnson and Johnson, Novo-Nordisk, Lilly Boerhinger, MSD, GSK, Astra Zéneca, Sanofi-Aventis, Novartis, BMS, Vertex.
PV: declares having received honoraria, grants and other fundings from Abbott, Bayer, Bristol Myers Squibb, AstraZeneca, Daichi-Sankyo, Eli-Lilly, GlaxoSmithKline, Kowa, Merck Santé, Merck-Sharp Dohme, Novo-Nordisk, Novartis, Pierre Fabre, Sanofi.
PD: declares having received funding from LVL médical, Bastide, Sanofi, Novo Nordisk, Lilly, MSD, Astra Zeneca, Boehringer Ingelheim, Abbott.
RT: declares having received grants from ResMed and other funding from AGIR à Dom.
PP: declares having received funding from Aliseo.
HH: declares having received funding from VitalAire.

FG: declares having received honoraria for consultancies, paid expert testimony, and other funding from Cidelec, Fisher & Paykel, Philips Respironics, ResMed, Sefam, VitalAire and Aliseo.


## Acknowledgments

We thank the Société francophone du diabète (SFD; French-Speaking Diabetes Society) for permitting the face-to-face meeting of all the authors of this paper. We also thank Johanna Robertson, native English medical writer, for critically reviewing the English language.


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