



Endocrine disorders in obstructive sleep apnoea syndrome: A bidirectional relationship

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Abstract

Obstructive sleep apnoea (OSA) is a common disorder characterized by recurrent episodes of apnoea or hypopnea due to total or partial pharyngeal collapse and temporary upper airway obstruction during sleep. The prevalence of OSA is increasing and currently affects about 30% of men and 13% of women in Europe. Intermittent hypoxia, oxidative stress, systemic inflammation, and sleep fragmentation resulting from OSA can provoke subsequent cardiometabolic disorders. The relationships between endocrine disorders and OSA are complex and bidirectional. Indeed, several endocrine disorders are risk factors for OSA. Compared with the general population, the prevalence of OSA is increased in patients with obesity, hypothyroidism, acromegaly, Cushing syndrome, and type 1 and 2 diabetes. In some cases, treatment of the underlying endocrine disorder can improve, and occasionally cure, OSA. On the other hand, OSA can also induce endocrine disorders, particularly glucose metabolism abnormalities. Whether continuous positive airway pressure (CPAP) treatment for OSA can improve these endocrine disturbances remains unclear due to the presence of several confounding factors. In this review, we discuss the current state-of-the-art based on the review of the current medical literature for key articles focusing on the bidirectional relationship between endocrine disorders and OSA and the effects of treatment. Screening of OSA in endocrine patients is also discussed, as it remains a subject of debate.

KEYWORDS

acromegaly, glucose intolerance, IGF-1, insulin resistance, obesity, obstructive sleep apnoea, sleep disordered breathing

1 | INTRODUCTION

Obstructive sleep apnoea (OSA) is a common disorder characterized by recurrent episodes of apnoea or hypopnea due to total or partial pharyngeal collapse and temporary upper airway (UA) obstruction during sleep, resulting in repeated episodes of hypoxaemia and hypercapnia. UA obstruction is typically caused by fat deposition in the parapharyngeal fat pads and pharyngeal muscles or abnormalities in craniofacial morphology. Arousal ensures pharynx reopening and

restores airflow, but it fragments sleep and alters its quality. Apnoea-hypopnea index (AHI) describes, on poly(somno)graphy (PSG), the number of obstructive events observed during 1 h of sleep. When associated with symptoms (e.g., excessive daytime sleepiness, choking, and snoring) or comorbidities, it is described as OSA syndrome (OSAS). AHI values of 5–14, 15–30, and more than 30 define mild, moderate, and severe OSAS, respectively. Intermittent hypoxia (IH) results in increased sympathetic activation and lead to increased risk for hypertension, arrhythmia, coronary heart disease, and stroke

in severe OSAS.¹ In the United States, the prevalence of moderate-to-severe OSAS is estimated, in adults 30–70 years of age, to be 13% among men and 6% among women.² This prevalence appears to be increasing as observed, for example, in a recent European study based on PSG in the general population that reported an estimated prevalence of 30% moderate-to-severe OSA in men and 13% in women.³ Continuous positive airway pressure (CPAP) remains the standard and most effective therapy for moderate-to-severe OSAS. CPAP has been proven to offer a survival benefit in patients with severe disease, to improve sleep quality and health-related quality of life, and to decrease cardiovascular events such as stroke and myocardial infarction.¹

Several endocrine disorders (e.g., obesity, acromegaly [AM], and hypothyroidism) are associated with a high frequency of OSA, and treatment of the underlying endocrine disorder can improve and occasionally cure OSA.

In this review, we discuss the current state-of-the-art based on review of the current medical literature for key articles focusing on the bidirectional relationship between endocrine disorders and OSA and the effects of treatment.

2 | ENDOCRINE RISK FACTORS FOR OSA

2.1 | Obesity

Obesity is one of the strongest sleep apnoea risk factors, with an odds ratio (OR) of disease occurrence of 4–10 compared with normal weight individuals.⁴ Epidemiologic studies have shown that the prevalence of OSA among individuals aged 30–49 years with a normal body mass index (BMI) < 25 kg/m² is 1.4%–7.0% but increases drastically for BMIs between 30 and 39.9 kg/m², to 13.5% (women) and 44.6% (men).² Overweight and obese OSA patients have a narrow UA, caused by fat deposition in the parapharyngeal fat pads and pharyngeal muscles.⁴

Obesity is also associated with a marked blunting of UA neuromuscular responses.⁵ It appears to be related to alterations in humoral factors, including ghrelin, adiponectin, and leptin, which have been associated with changes in body weight and regional adiposity.⁵

In addition, OSA may aggravate weight gain and obesity comorbidities. Both conditions lead to an increase in the risk of cardiovascular events and mortality,¹ and increased risk of cancer is also observed for obesity.⁶ There is a bidirectional relationship between OSA and obesity, creating a destructive cycle. In the majority of studies, BMI is used to determine the relationship between OSA and obesity but it is important to specify that BMI alone is not a good predictor of OSA in obese patients because OSA is mainly associated with central distribution of body fat. Increased waist circumference, waist-to-hip ratio, and neck circumference (NC) have been shown to be associated with higher OSA prevalence. In particular, increased NC is associated with OSA and metabolic syndrome (MS), independent of waist girth.⁷ The effect of obesity on OSA susceptibility is related to the distribution of adiposity between the central and

peripheral compartments. Central obesity explains the high male predominance of this disorder, whereas peripheral adiposity may protect women from developing OSA before menopause. Indeed, hormonal changes related to obesity can also impact on OSA susceptibility, particularly in women. Androgens play a significant role in the pathogenesis of OSA in obese women with polycystic ovary syndrome (PCOS), in whom the prevalence of OSA exceeds that of identically obese women without this disorder. Moreover, the severity of OSA in PCOS is related to the serum androgen concentrations, suggesting that male sex hormones promote its development.⁵

In fact, free testosterone levels higher than 1.07 ng/dl was demonstrated as an OSA predictor (odds ratio [OR] = 8.2, 95% confidence interval [CI]: 1.3–49.7, *p* = .023).⁸

Obesity is also a common cause of resistant hypertension. An excessive production of aldosterone in obese patients has been demonstrated.⁷ Growth hormone (GH) and insulin growth factor-1 (IGF-1) levels are reduced in obese patients,⁹ and low IGF-1 levels correlated with increased AHI.¹⁰

Abdominal obesity has also been considered as the link between OSA and metabolic disturbances. IR is commonly associated with abdominal obesity. In this situation, biological action of insulin is reduced and provokes finally diabetes, a risk factor for OSA.

With the current obesity epidemic, that is provoked by multiple factors (e.g., genetic, family history, socioeconomic, and sociocultural conditions), the prevalence of OSA is likely to increase.

2.2 | Hypothyroidism

The prevalence of OSA in patients with overt (OH) or subclinical (SCH) hypothyroidism is currently not well known due to heterogeneity in definitions of hypothyroidism, BMI, gender, and lack of information on the presence of thyroid autoimmunity and goitres. However, in a recent systematic review, the prevalence of OSA was estimated to be 25%–50% in patients with OH.¹¹ There are many different mechanisms that may explain this association between OH and OSA, and these are mainly related to changes in respiratory physiology. The most important is the disturbance of the regulatory control of pharyngeal dilator muscles due to neuropathy and the possibility of respiratory centre depression.¹² In severe myxedema, macroglossia and deposition of mucoproteins in the UA can also cause UA obstruction.¹¹ Despite the fact that SCH has been associated with a higher prevalence of atherosclerosis, higher lipid profiles, and insulin resistance, the link between SCH and OSA is not comparable to that of OH due to the absence of severe impacts of SCH on respiratory physiology. SCH patients may have reduced diaphragmatic muscle strength and lower lung volumes but this does not contribute to OSA.¹¹ However, large goitres present in some patients with OH can cause UA obstruction and OSA by mechanical compression (UA oedema caused by decreased venous return from head and neck), independently of thyroid dysfunction.¹³ Thus, OH can directly cause OSA but may also contribute through its impact on the MS.^{11,14,15}

2.3 | Acromegaly

OSA is found in 69% of patients with active AM. AM induces facial skeletal deformities (mostly mandible enlargement), and pharyngeal/tongue thickening due to glycosaminoglycan deposition and increased collagen production by connective tissue. Tissue oedema also contributes to OSA and is caused by increased renal sodium reabsorption due to the direct stimulation of epithelial sodium channels by GH and IGF-1. Overweight, frequently associated with AM, increases the risk of OSA even more.¹⁶ The prevalence of AM in OSA patients has been shown recently to be 0.14%–0.71%, much higher than in the general population.¹⁷

Central sleep apnoea (CSA) are also occurring in AM but less frequently than OSA. They are related to increased ventilatory response to carbon dioxide and are observed in patients with higher GH and IGF-1 levels.^{18,19}

2.4 | Cushing syndrome (CS)

CS is associated with obesity and diabetes and leads to a 2.82-fold higher risk of OSA (hazard ratio [HR] = 2.82; 95% CI: 1.67–4.77).²⁰ This association is not only related to obesity in CS. Indeed, in a case–control study comparing people with CS to gender-, age-, and BMI-matched controls, the prevalence of OSA was twofold higher in CS than in controls. Adipose tissue accumulation in the subcutaneous tissue of the neck and muscle weakness that characterize CS may be involved in UA narrowing during sleep and susceptibility to developing OSA.²¹

2.5 | Diabetes

2.5.1 | Diabetes mellitus–type 2

OSA is very prevalent among patients with type 2 diabetes mellitus (T2D), affecting 24%–86%, significantly more than in the nondiabetic population.²² A recent, large retrospective case–control study showed that T2D patients had a relative risk (RR) of 1.76 (95% CI: 1.69–1.84) of developing incident OSA during a 15-month follow-up period compared with nondiabetics. The association remained significant (RR: 1.48; 95% CI: 1.42–1.55) after adjustment for confounders (e.g., age, sex, and BMI).²²

There are a number of factors that might provide a pathophysiological link between T2D and OSA. For example, T2D might lead to the development of OSA as a result of the effect of IR and autonomic nervous system dysfunction, impacting UA stability.²³ T2D may also worsen OSA by altered responsiveness of the carotid body (CB) when exposed to chronic hyperglycaemia: this toxic exposure attenuates CB discharge rate and causes CB degeneration, which can lead to reduced reactivity to

hypoxaemia.²⁴ Besides, increased HbA1c levels have been shown to correlate with increased OSA severity.²⁵

Another pathophysiological mechanism that is likely to be involved in OSA development is autonomic neuropathy. In particular, T2D may have an impact on the chemical control of breathing by affecting central and peripheral chemoreceptors and glossopharyngeal, vagal, and proprioceptive nerves to aggravate or induce OSA.²⁶ Indeed, it has been shown that, compared with patients free from diabetic peripheral neuropathy (DPN) and matched control, T2D patients with DPN were significantly more affected by OSA. Moreover, a positive correlation between DPN severity and OSA severity was highlighted.²⁷

In a recent cross-sectional Chinese study, more severe OSA correlates with the presence of microvascular complications (DPN, diabetic retinopathy, and diabetic nephropathy), suggesting a role in OSA development.²⁸

Due to the high prevalence of OSA in T2D patients, the International Diabetes Federation states that all patients with T2D should be screened for OSA.²⁹

2.5.2 | Diabetes mellitus–type 1

The high prevalence of OSA reported in type 1 diabetes mellitus (T1D) confirms that OSA in diabetes is not only related to increased BMI but also to hyperglycaemia and its microvascular and macrovascular complications.³⁰

The prevalence of moderate-to-severe OSA is 10.3% in T1D after 9.3 ± 7.3 years of disease but rises to 46.3% in long-standing T1D (29 ± 14 years).³¹

2.6 | Primary aldosteronism (PA)

PA and OSA share the same risk factor, namely obesity. Excess fat tissue exacerbates OSA and adipocyte secretory products induce aldosterone oversecretion in subjects with obesity.³² PA generates fluid overload and metabolic abnormalities that contribute to the development of OSA. Fluid displacement into neck structures from the lower limbs can lead to soft tissue oedema and cause UA resistance and airflow obstruction. Indeed, nocturnal rostral fluid shift is one of the mechanisms implicated in OSA and CSA occurrence in heart failure.³³ OSA is common in patients with PA, ranging from 8% to 11% of patients, but is not much different than that of the general population. In the recent cross-sectional HYPNOS study,³⁴ a significant association between plasma aldosterone levels and moderate-to-severe OSA diagnosis was found in White patients, but the OR was very low, 1.002 (95% CI: 1.001–1.003), challenging the guidelines of the Endocrine Society stating that PA should be screened for in OSA patients with hypertension.³⁵

Figure 1 summarizes OSA prevalence in endocrine disorders.

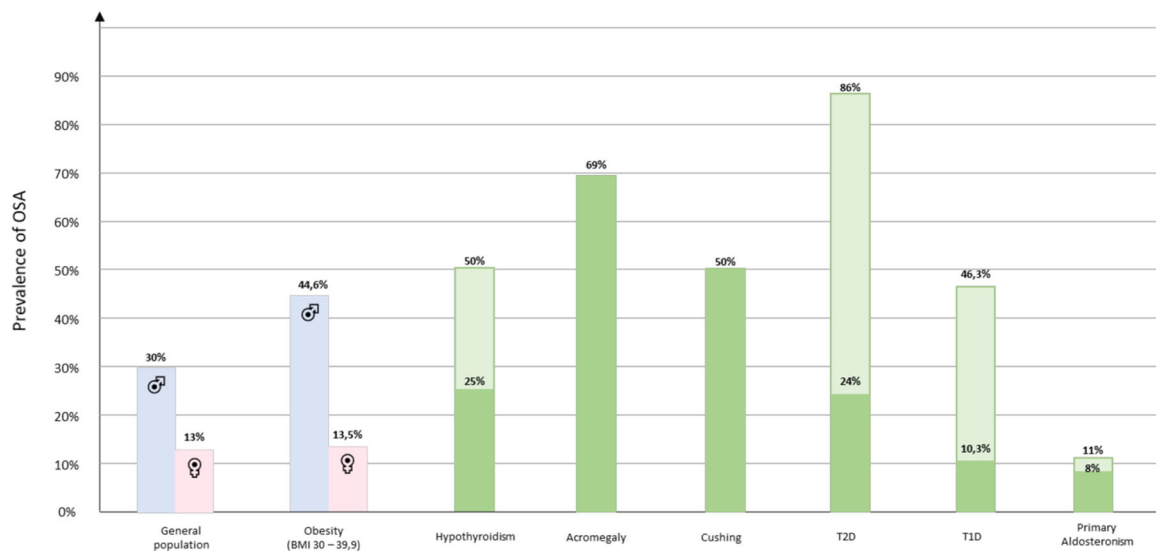


FIGURE 1 Obstructive sleep apnoea (OSA) prevalence ranges in endocrine and metabolic disorders. Shading on columns represents the extent of prevalence of OSA in the different endocrine disorders. ♂, male; ♀, female; BMI, body mass index; OSA, obstructive sleep apnoea; T2D, diabetes mellitus 2; T1D, type 1 diabetes mellitus

3 | ENDOCRINE DISORDERS INDUCED BY OSA

3.1 | Pathophysiological mechanisms responsible for the relationship between OSA and endocrine disorders

Pathophysiology of OSA is complex, implying different mechanisms as UA collapsibility (depending from the ability to collapse, anatomically narrowed UA), UA muscles capability to dilate in case of narrowing, arousals from sleep in response to increased respiratory drive and ventilatory loop gain. These mechanisms lead to heterogeneous UA reaction to hypopnea and apnoea among mild-to-severe OSA patients, and can be individually assessed through the passive critical closing pressure of the upper airway, arousal threshold, loop gain, and muscle responsiveness scale, aiming to phenotype OSA patients.³⁶

Consequences imply that partial or complete UA collapse induces repeated drops in oxygen saturation, cardiovascular perturbations (tachycardia, bradycardia, and increased blood pressure), and sleep fragmentation provoked by arousals.

OSA impacts endocrine systems, and it seems to be mediated by IH, sympathetic activation, arousals, and systemic inflammation.

3.2 | Endocrine biochemistry modifications induced by OSA

Sleep onset and slow wave sleep (SWS) are associated with a decline in cortisol levels followed by increased cortisol secretion in late sleep and morning awakening.

In a systematic review of studies that compared cortisol levels in patients with OSA to either obese or lean control, there was no

evidence of hypothalamic–pituitary–adrenal (HPA) activation in patients with OSA in 6/7 studies.³⁷ However, only two of these studies had plasma cortisol measurements over 24 h, and reported contradicting results. It could be that the impact of OSA on HPA axis may not be related to basal or 24-h cortisol profiles but might be related to the dynamic responses to HPA inhibition or stimulation. Carneiro et al. showed that although basal salivary cortisol was not different between patients with OSA versus obese controls, the salivary cortisol inhibition following overnight dexamethasone suppression test was significantly less pronounced in patients with OSA compared with obese controls.³⁸

In a recent meta-analysis, no significant relationship between OSA and plasma renin activity/concentration was observed but angiotensin II levels were significantly higher in patients with OSA compared with controls.³⁹

Regarding GH secretion, studies in rodents and humans suggest that OSA is associated with suppression of basal and stimulated GH and IGF1 levels.⁴⁰

Pseudophaeochromocytoma patterns have been observed in patients with OSA and hypertension. They present with clinical and biochemical features of phaeochromocytoma without the presence of a catecholamine secreting tumour. These cases are rare but have been reported in multiple case reports and series, and the clinical and biochemical features usually resolve with CPAP treatment or weight loss.^{41,42}

3.3 | Glucose metabolism

Focusing on glucose metabolism, several pathophysiological links have been reported. First, IH may affect glucose metabolism by inducing sympathetic activation, systemic inflammation with pro-

inflammatory cytokines secretion, increasing counter-regulatory hormones and fatty acids, and provoking on one hand IR and on the other pancreatic β cell dysfunction, increasing with OSA severity.^{43,44} Second, sleep fragmentation also increases sympathetic activity and alters the HPA axis, leading to IR. In addition, sleep structure can also contribute to IR because the suppression of SWS has been shown to increase IR. SWS deprivation is a usual trait of OSA.³¹ Moreover, there is a dose-dependant effect of OSA, with more IR observed in severe OSA⁴⁵ independently of obesity and fat mass.

Increased fasting glucose levels and incident T2D, related to OSA and its severity, have been observed in cross-sectional, observational, and retrospective studies.⁴⁶ Increased CB chemosensitivity occurring in OSA is another mechanism leading to increased sympathetic activity, high blood pressure and dysregulation of peripheral insulin sensitivity and glucose homeostasis.⁴⁶ As prediabetes and T2D increase also CB sensitivity,⁴⁷ a negative metabolic vicious circle occurs in OSA.

Partial sleep deprivation induces also dysfunction of the HPA axis and sympathetic activation, impairing glucose homeostasis.

In a meta-analysis conducted by Anothaisintawee et al., OSA was found to be an independent risk factor for T2D after adjustment for age, sex, and BMI with a RR of 2.02 (95% CI: 1.57–2.61).⁴⁸ Another recent study showed that glucose metabolism disorders in OSA may go unrecognized and that 28% of moderate-to-severe OSA patients have undiagnosed glucose intolerance (GIT) or T2D.⁴⁹

Systematic screening should be proposed in this population who have a lot of comorbidities and who meet the criteria for testing for diabetes or prediabetes according to American Diabetes Association (ADA) guidelines.⁵⁰

3.4 | Thyroid function

Whether OSA is associated with an increased prevalence of thyroid disorders remains controversial. A recent meta-analysis that included 17 studies showed an increased prevalence of OH in OSA (8% vs. an estimated prevalence in Europe in the general population of 0.5%–5.2%). OH occurrence was associated with OSA severity. No increased prevalence was found for SCH. The main confounding factor in this population is obesity.^{51,52}

Indeed, the prevalence of thyroid dysfunction and thyroid autoimmunity is higher in obese people.¹³ Bozkurt et al. conducted a study on the prevalence of autoimmune thyroiditis, in euthyroid subjects with a suspicion of OSA.⁵³ Autoimmune thyroiditis was defined as positivity for Anti-TPO and/or Anti-TG and patients with thyroid parenchymal heterogeneity and reduced echogenicity. Autoimmune thyroiditis was diagnosed in 47% of OSA patients and in 32% of controls; the prevalence was high in OSA and controls in that study, probably, because it was performed in Japan, an area with a higher prevalence of thyroid autoimmunity than in other regions in the world, due to the high iodine intake.⁵⁴

The high prevalence of 47% in patients with OSA may be explained by the fact that OSA is associated with a low grade systemic

inflammation, induced by IH, and that on its turn that may induce cellular injury and upregulation of an immune response to intracellular antigens via the exposure of antigen presenting cells and as such lead to autoimmune diseases.^{55,56}

The authors concluded that Hashimoto's disease prevalence was increased in OSA, and correlated with the severity of OSA. The association was stronger among women.⁵³

There are several mechanisms that may lead to increased thyroid stimulating hormone (TSH) levels in obesity. Adipose tissue produces cytokines and other inflammatory factors, and leptin increases thyrotropin-releasing hormone (TRH) levels through a direct action on TRH neurons. Furthermore, increased deiodinase activity has been described in obesity, which leads to a higher conversion of T4–T3.¹⁴ Finally, obesity has been associated with a higher prevalence of thyroperoxydase antibodies.⁵⁷ Further studies are needed to explore the pathophysiological links between OSA and OH in more detail.

3.5 | Hypogonadism

Dysfunction of the hypothalamic–pituitary–gonadal (HPG) axis in response to high cortisol levels (HPA dysfunction) should lead to increased testosterone. However, level seems to be normal or decreased, because also influenced by hypoxia provoked by OSA, independently of increasing age or obesity.^{13,58}

In a recent case–control study, the presence of OSA in males was associated with lower testosterone levels, especially in more severe OSA.⁵⁹ Dysfunction of the HPG axis leading to lower levels of total and free testosterone also seems to be linked to hypoxia provoked by OSA, independently of increasing age or obesity.¹³ In females, AHI > 10 is associated with lower serum levels of 17-OH progesterone, progesterone, and estradiol, suggesting that OSA might impair ovarian function.⁶⁰

3.6 | Hyperaldosteronism

A potential bidirectional relationship between OSA and hyperaldosteronism has been evoked, as hyperaldosteronism can cause OSA, but OSA can also induce the activation of the renin–angiotensin–aldosterone system (RAAS) via IH,⁶¹ leading to additional increase in hormonal level.

3.7 | Impact of OSA severity on endocrine disturbances

The exact role of OSA severity on endocrine disturbances seems difficult to establish because of confounding factors (e.g., obesity in OH) or lack of data. However, in glucose metabolism disorders, it seems that T2D and GIT are not associated with the severity of the OSA, contrarily to IR.⁴⁹

4 | IMPACT OF TREATMENT

4.1 | Can OSA improve/be cured by treating underlying endocrine disorders?

4.1.1 | Obesity

It is now well documented that weight reduction leads to OSA improvement in obese patients. Sarkhosh et al. reviewed the impact of bariatric surgery (restrictive procedures, restrictive with a mild malabsorptive component, or largely malabsorptive procedures) on OSA in 13,900 patients. According to the different procedures, OSA improvement or resolution was obtained in 78%–90% of the patients.⁶² Predictive factors for persistent moderate-to-severe OSA after weight loss surgery include age ≥ 50 years, preoperative AHI ≥ 30 , excess weight loss $< 60\%$, and hypertension.⁶³

Weight loss remains a highly effective strategy for treating sleep apnoea. The reduction of 10%–15% in body weight leads to an approximately 50% reduction in sleep apnoea severity (AHI) in moderately obese male patients. The weight loss decreases the UA collapsibility during sleep, which can be attributed to reductions in mechanical loads or improvements in pharyngeal neuromuscular control.⁵

4.1.2 | Hypothyroidism

Thyroid hormone replacement therapy is usually accompanied by normalization of thyroid function and also by improvement in BMI, skinfold thickness, blood glucose, and serum lipids, and may improve OSA in OH. However, this favourable outcome was observed only in a few, old studies with a limited number of patients, highlighting a significant reduction in apnoea periods, ODI, snoring, and choking. OSA resolution was obtained in 66%.^{64–67} However, since several factors contribute to OSA (e.g., male sex, menopausal status in women, age, and obesity), it seems clear that hormone replacement therapy for OH alone is not sufficient to resolve OSA.

4.1.3 | AM

Treating AM can help to resolve or improve OSA in many patients but up to 40% exhibit persistent OSA, despite good disease control. Therefore, OSA should be closely monitored (clinically and by polysomnography) after AM treatment initiation.⁶⁸ In AM, excess GH has a direct effect on UA narrowing, inducing overgrowth of mandible and maxilla bones, pharyngeal soft tissue swelling, and macroglossia. These factors may be partially reversible after the treatment of AM but not in all patients.⁶⁹ Once more, excess weight or associated OH can contribute to the persistence of the disorder.⁷⁰

4.1.4 | CS

No specific literature is yet available regarding the effect of CS treatment on OSA.

4.1.5 | Diabetes mellitus–type 2

A recent Spanish study addressed the question on the impact of glucose improvement on nocturnal sleep breathing parameters in patients with T2D. In this interventional study, 35 T2D/OSA patients underwent home polysomnography at baseline and after a 4-month period in which antidiabetic therapy was intensified to improve glycaemic control (with metformin alone [11.4%] or with other oral agents [22.9%], basal insulin alone or with basal-bolus regimen [25.7%], glucagon-like peptide-1 [GLP-1] receptor agonists plus oral agents [5.7%], and basal insulin associated with GLP-1 [8.6%]). Moreover, to minimize the effect of weight loss on the results, patients who reduced their BMI by more than 2.0 kg/m² were excluded. Modest improvements in AHI and nocturnal hypoxaemia were observed in the 24 good responders (HbA1c reduction $\geq 0.5\%$). Better results were obtained in patients treated by insulin alone. These interesting data need to be confirmed in further studies.⁷¹

4.1.6 | PA

Small observational studies and randomized controlled trials have shown, in patients with resistant hypertension and OSA, that aldosterone antagonist blockade medications resulted in significant reduction of AHI.³² The effect on OSA seems to result from a reduction in NC.⁷²

4.2 | Does CPAP improve the endocrine consequence of OSA?

CPAP is the cornerstone of OSA therapy. CPAP devices apply continuous air pressure to keep the upper airway open, allowing patients to breathe adequately during the night. CPAP use has been associated with better sleep efficiency, fewer arousals, lower AHI, and less oxygen desaturation.

4.2.1 | Hypothyroidism

In a study by Petrone et al., patients with moderate-to-severe OSA had a 10.4% prevalence of nonthyroidal illness syndrome (NTIS) (normal TSH with low triiodotironine) and an 8% prevalence of SCH. Patients with NTIS had worse nocturnal hypoxaemia than the other OSA subjects. Treatment of OSA led to an improvement in hormone levels in both NTIS and SCH patients. Indeed, under CPAP therapy,

100% of patients with NTIS had T3 levels increase to the normal range, and 75% of SCH had a decrease in TSH levels.⁷³

4.2.2 | Diabetes mellitus–type 2

It is not clear whether CPAP has a favourable effect on glucose metabolism. Current available data in the literature report contradictory results, and the effect of CPAP on glycaemic control remains debatable. Recently, based on the results of the SAVE study in a population of 888 patients with OSA and stable cardiovascular disease in which patients were followed for HbA1c at baseline and at 2 and 4 years, it was found that CPAP therapy did not affect glycaemic control in those with T2D or prediabetes or diabetes risk over usual care treatment.⁷⁴ In addition, in a recent meta-analysis including 443 participants, CPAP treatment (duration of CPAP intervention >2 weeks) significantly improved IR, measured by homeostasis model assessment of insuline resistance index, but not fasting glucose levels.⁷⁵ Furthermore, the only randomized study involving patients with T2D and OSA who were treated for 3 months with CPAP or sham CPAP was not able to demonstrate a positive effect of CPAP on HbA1C or IR.⁷⁶ Multiple factors may contribute to the difficulty of isolating the effect of CPAP on metabolic aspects of OSA including different levels of CPAP adherence, glycaemic control, the use of antidiabetic drugs, disease progression, sedentarity, obesity, and diet, among others. These discrepancies among studies clearly indicate that more research on the effects of CPAP on glycaemic control is required, but biases will be difficult to avoid.

4.2.3 | CS/cortisol levels

CPAP treatment in individuals with OSA can reduce cortisol levels and blood pressure. Patients with suspected CS and suffering from hypertension would benefit from an initial screening for OSA and should proceed to a sleep study, if indicated. If OSA is present, CPAP treatment may help to avoid a false-positive diagnosis of CS (pseudo-CS) and can also lower blood pressure. The impact of CPAP on cortisol and blood pressure has been debatable because of conflicting findings between studies due to variation in study designs and small sample sizes. These findings suggest that CPAP reduces stress induced by OSA. In response, secretion of stress hormones such as cortisol and catecholamines is also decreased and have an impact on blood pressure. Identification and treatment of such patients is important when investigating for suspected CS and hypertension.⁷⁷

5 | DISCUSSION

In this review, we have discussed the bidirectional links between OSA and endocrine disorders. While there are sufficient scientific arguments to be confident with regard to a likely causal link between OH, AM, and diabetes as risk factors for OSA, the evidence is less clear for

others, such as PA and CS, because of low numbers of publications (rare diseases) or because of the difficulty of isolating a 'pure' effect of these endocrine disorders in patients who suffer from many other risk factors for OSA, such as obesity, sedentarity, or aging.^{4,78}

The connection between OSA and obesity is very complex. Although it is well known that obesity contributes to OSA development, recent evidence suggests that OSA can also aggravate weight gain and obesity comorbidities. Together, both conditions lead to dramatic increases in the risk of cardiovascular events and mortality.⁷ The perturbation of glucose and lipid metabolism in obese patients can also aggravate OSA. Unfortunately, in studies, these variables are generally not taken into account separately from obesity. A final caveat concerns the assessment of obesity, as the majority of studies have focused on BMI, but given the impact of fat distribution on endocrine/metabolic disturbances and OSA, measures of central fat mass would have been more appropriate.

Regarding the possibility of reversing OSA by treating the underlying disease, evidence is available for obesity and AM but not formally for the other diseases due to the paucity of available data.

The reverse is also true for the endocrine consequences of OSA. Dating the precise start of a disease (OSA, hypothyroidism, and T2D) is often difficult and can make it impossible to distinguish an OSA-associated preexisting disorder from a new one caused by it.

To understand better the relationship between OSA and thyroid, in both directions, ideally, longitudinal prospective studies should be done with corrections for the presence of goitre and thyroid antibodies.

For the prevalence of OSA in patients with (SCH) hypothyroidism, the follow-up should start from the moment that the thyroid dysfunction is diagnosed. However, before a thyroid disorder is detected clinically or biologically, it is probably already present for some months to years in a slight form, also characterized by the fact that patients are already treated with LT4.

Concerning the prevalence of thyroid disorders in OSA patients, longitudinal prospective studies are also needed to observe the development of (SCH) hypothyroidism in patients without known thyroid disorders and starting when OSA is diagnosed. Corrections for other parameters that determine high TSH, like BMI and thyroid antibodies should be made.

Despite this barrier, it now seems well proven that OSA induces glucose metabolism disorders, but more data should be obtained regarding hypogonadism and thyroid disorders. The effect of CPAP on OSA-associated disorders is not clear in the majority of studies. Indeed, apart from CPAP adherence,⁷⁹ it is difficult to isolate the 'pure' effect of CPAP due to the many confounders that additionally influence (positively or negatively) its effects: sedentarity, aging, diabetes, and dyslipidaemia treatment characteristics (choice, effectiveness, and adherence).⁴⁶ The lesser effect of CPAP on the reversibility of disorders associated with OSA could also be due to the small impact of OSA on the disease itself. Indeed, OSA is rarely the only risk factor for endocrine disorders in these multimorbid patients. The question of screening also remains open. Criteria for screening have been developed by the World Health Organization. The

importance of the health problem should be certain. The screening test should be simple, specific, and sensitive, and early treatment (accepted/effective) of the disease should significantly influence the future of health of the patient. The harm/benefit ratio should be low and the screening must be cost-effective.⁸⁰

Should we screen endocrine patients for OSA? Systematic evaluation of the risk of OSA in patients with type 2 diabetes may be recommended because the treatment of potential OSA may help to manage diabetes and other cardiovascular risk factors in these patients. In 2008, the International Diabetes Federation (IDF) taskforce recommended a targeted approach to screening for OSA in obese patients with T2D since 24%–86% patients with T2D have OSA. IDF proposed that T2D patients be screened if they are suffering from classical OSA symptoms (witnessed apnoeas, heavy snoring, or daytime sleepiness).²⁹ However, despite the background scientific evidence supporting this recommendation, it does not seem to be applied by diabetes physicians and endocrinologists, who are sometimes not aware of the IDF recommendation.⁸¹

Screening for OSA in AM and OH would also seem to be very useful due to the very high prevalence of OSA in these populations and the uncertain course of the disease after treatment (OH) or documented persistent OSA in a significant proportion of treated AM patients.

In obesity, the latest release from the US Preventive Services Task Force stated that there is insufficient evidence to screen for or treat OSA in asymptomatic adults or adults with unrecognized symptoms.⁸² However, it is accepted that all patients undergoing bariatric surgery should be screened for OSA and obesity hypoventilation syndrome to reduce the risk of perioperative complications.^{81,83} Simple clinical measurements, as NC, could also be used to suspect OSA in patients. Indeed, in men, a NC > 42.3 cm predicts the presence of moderate-to-severe OSA with an accuracy of 78%.⁸⁴

In contrast, regarding the latest available data on PA that confirmed a similar PA prevalence in OSA and the general population, there is no longer a need to screen for PA in OSA patients with hypertension, as formerly recommended by Endocrine Society in 2016.³⁵

Should we screen OSA patients for endocrine disorders? Concerning thyroid disorders, a diagnosis of SCH is simple and consists of measurement of TSH and FT4. Before patients are suffering from OH, at the SCH stage, they are often asymptomatic. Screening for thyroid function has been estimated to be cost-effective in a setting of pregnancy, even if only OH disease is considered.⁸⁵ However, for the general population, the Preventive Services Task Force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.⁸⁶ The debate is still open and should rely on more scientific evidence in the future, based on long-term, large group follow-up studies to establish the possible significance of routine evaluation for thyroid disease in OSA patients. We should continue to perform case finding in OSA for examples in high-risk groups (i.e., older women) or in patients who are overtly symptomatic.

Screening for AM in OSA appears to be an option for optimizing the detection rate due to the fact that, in that situation, the prevalence of AM is 8–30-fold higher compared with that in the general

population.¹⁶ In AM, the screening should be targeted, according to the presence of concomitant comorbidities and/or clinical features of AM. In Endocrine Society guidelines, it is suggested that IGF-1 be measured in all patients with typical manifestations of AM.¹⁷ Physicians caring for OSA patients should be aware of these features. In patients with OSA, it has been suggested that IGF-1 be measured only if other comorbidities, such as diabetes and hypertension, are present too.⁸⁷ Indeed, the systematic measurement of IGF-1 might not be the most optimal cost-benefit approach to detect AM and, therefore, novel techniques to detect AM are urgently needed. One option could be the recognition of mild dysmorphic features by computer software using photographs of the face and, in the near future, artificial intelligence, using deep-learning algorithms.⁸⁸

There are currently no recommendations to screen for diabetes in OSA. However, ADA recommends diabetes screening in overweight or obese patient who have one or more risk factors (first-degree relative with diabetes, high-risk ethnicity [e.g., African American], history of cardiovascular disorder, hypertension, low high density lipoproteins level, high triglyceride level, women with PCOS, physical inactivity, and other clinical conditions associated with IR).⁵⁰

Many OSA patients exhibit at least one of these characteristics and should be screened for glucose metabolism disorders. More investigation with surveys are needed to know if these guidelines are currently applied.

6 | CONCLUSIONS

OSA is a very prevalent disease that should be actively screened for in type 2 diabetes mellitus, AM, CS, and OH hypothyroidism seen its high prevalence in these disorders. Conversely, OSA induces several endocrine alterations that need to be screened in OSA patients. Screening for AM is not yet recommended but should be further studied. Signs of AM should be particularly explored by the somnologist when assessing a newly diagnosed OSA patient to avoid misdiagnosis and long-term consequences of an untreated disease. Screening for thyroid disorders remains more controversial but case finding, especially in symptomatic or at-risk patients, is certainly valuable. Detecting endocrine disorders associated with OSA is of importance as treatment can help improve OSA. On the other hand, the effect of CPAP treatment of OSA seems very limited for reducing the burden of endocrine diseases because of its multifactorial aspect.

ACKNOWLEDGEMENTS

The authors acknowledge the contribution of a medical writer, Sandy Field, PhD, for English language editing and formatting of this manuscript.

CONFLICT OF INTERESTS

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other

equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

AUTHOR CONTRIBUTIONS

All the authors wrote a part of the present manuscript. Maud Akset and Marie Bruyneel prepared the figures, Maud Akset, Marie Bruyneel and Kris Gustave Poppe prepared the final version of the manuscript, approved by all the authors.

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How to cite this article: Akset M, Poppe KG, Kleynen P, Bold I, Bruyneel M. Endocrine disorders in obstructive sleep apnoea syndrome: a bidirectional relationship. *Clin Endocrinol (Oxf).* 2023;98:3-13. doi:10.1111/cen.14685