MECHANISMS OF ENDOCRINOLOGY

Mechanisms of disease: the endocrinology of obstructive sleep apnoea

Aikaterini Lavrentaki¹, Asad Ali², Brendan G Cooper³,⁴ and Abd A Tahrani¹,⁵,⁶

¹Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK, ²Department of Respiratory Medicine, University Hospitals of Coventry and Warwickshire NHS Trust, Coventry, UK, ³Department of Respiratory Medicine, University Hospitals of Birmingham NHS Foundation Trust, Birmingham, UK, ⁴Institute of Clinical Sciences, University of Birmingham, Birmingham, UK, ⁵Centre of Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK, and ⁶Department of Endocrinology, University Hospitals of Birmingham NHS Foundation Trust, Birmingham, UK

Abstract

Obstructive sleep apnoea (OSA) is a common disorder that is associated with serious comorbidities with a negative impact on quality of life, life expectancy and health costs. As OSA is related to obesity and is associated with sleep disruption, increased inflammation and oxidative stress, it is not surprising that OSA has an impact on the secretion of multiple hormones and is implicated in the development of many endocrine conditions. On the other hand, many endocrine conditions that can affect obesity and/or upper airways anatomy and stability have been implicated in the development or worsening of OSA. This bidirectional relationship between OSA and the endocrine system has been increasingly recognised in experimental and epidemiological studies and there are an increasing number of studies examining the effects of OSA treatment on endocrine conditions and vice versa. In this review article, we will critically appraise and describe the impact of OSA on the endocrine system including obesity, dysglycaemia, the pituitary, the thyroid, the adrenals, the reproductive system and the bones. In each section, we will assess whether a bidirectional relationship exists, and we will describe the potential underlying mechanisms. We have focused more on recent studies and randomised controlled trials where available and attempted to provide the information within clinical context and relevance.

Invited Author’s profile

Abd A Tahrani is a National Institute for Health Research (NIHR) Clinician Scientist at the University of Birmingham (UoB), an Honorary Consultant Endocrinologist at the University Hospitals of Birmingham NHS Foundation Trust, the lead for weight management research and diabetic neuropathy services at Birmingham Heartlands Hospital, the lead for translational research in the Centre of Endocrinology, Diabetes and Metabolism (CEDAM), Birmingham Health Partners and the communication co-lead in the Institute of Metabolism and Systems Research (IMSR) at the UoB. He obtained his PhD in 2013 from UoB, which was focused on the impact of obstructive sleep apnoea (OSA) in patients with type 2 diabetes and was awarded a SCOPE National Fellowship in 2014 from the World Obesity Federation. Abd’s research has the following themes: the metabolic consequences of sleep-related disorders, obesity management and complications, diabetes-related neuropathy and the pharmacology of type 2 diabetes and obesity.
Introduction

Obstructive sleep apnoea (OSA) is a common disorder that affects 13–33% of men and 6–19% of women (1). OSA is characterised by instability in the upper airways (UAs) leading to recurrent episodes of the UA obstruction, particularly during the transition to sleep and rapid eye movement (REM) sleep (characterised by low-amplitude, mixed-frequency theta EEG waves, pronounced eye activity and low muscle tone (2)) (Supplementary data, see section on supplementary data given at the end of this article) (3, 4, 5, 6). These repeated obstructions are associated with recurrent episodes of oxygen desaturation/re-saturation, cyclical changes in blood pressure (BP), heart rate, sympathetic activity and intrathoracic pressure, brief microarousals and changes to sleep architecture, such as the loss of REM and slow wave sleep (SWS or deep sleep is stage N3 of NREM sleep characterised by high-amplitude slow waves, further decrease in muscle tone, possible eye movement cessation and is a restorative sleep stage decreasing though with age (2)) (Fig. 1 and Supplementary data) (3, 5, 7).

The interactions between OSA and the endocrine system have attracted much attention and they often can be bidirectional, which is not surprising considering the diurnal secretion pattern of many hormones. In addition, OSA treatment (namely continuous positive airway pressure CPAP) has an impact on the endocrine system (such as insulin resistance, cortisol secretion) while treating endocrine disorders (such as obesity, hypothyroidism or acromegaly) can also improve OSA. Moreover, the well-established higher OSA risk in men vs women also emphasises the potential relationship between sex hormones and OSA pathogenesis. Hence, it is important to understand the links between OSA and the endocrine/metabolic system in order to improve our understanding of the pathogenesis and the comorbidities and mortality associated with OSA and a variety of endocrine disorders (8).

In this article, we will review the interactions between OSA and the endocrine system, and we will highlight the underlying mechanisms underpinning this bidirectional relationship when exists, as well as explore the potential impact of OSA treatment on the endocrine disorders and vice versa. Some aspects of this article require some understanding of the pathogenesis of OSA; hence, we have provided an overview of OSA and its pathogenesis in the Supplementary data.

OSA and obesity interplay

Obesity is a major risk factor for the development of OSA (9, 10, 11), which is driving the increase in OSA prevalence (1, 12). Obesity prevalence in patients with OSA (approx. 70%) is also higher than that of the general population (13).

The impact of weight change on OSA

Weight changes have significant impact on OSA and its severity. In a longitudinal study of randomly selected patients from Wisconsin, a 10% weight gain over 4 years was associated with 32% (95% CI 20–45%) increase in the apnoea–hypopnoea index (AHI: the average number of apnoea and hypopnea events per hour of sleep) and six-fold higher risk of developing moderate-to-severe OSA (95% CI 2.2–17) compared to weight stability (11). On the other hand, 10% weight loss was associated with 26% (95% CI 18–34%) decrease in the AHI compared to weight stability (11), partly due to a reduction in UAs collapsibility observed with weight loss (14). The favourable impact of weight loss on OSA and its severity seems to be evident regardless of the method of losing weight such as lifestyle interventions, pharmacotherapy or bariatric surgery as has been shown by several studies among them and randomised controlled trials (RCTs) (14, 15, 16, 17, 18).

In a RCT, of 60 patients with obesity and moderate-to-severe OSA, laparoscopic adjustable gastric banding (LAGB) resulted in greater weight loss (5.1 vs 27.8 kg) and greater reductions in AHI (based on PSG) (−14.0 vs −25.5

Figure 1

Hypnograms and sleep stages of a healthy individual (top) and a patient with OSA (bottom). Please note how the patient with OSA has disrupted sleep architecture with loss of REM and SWS. REM, rapid eye movement; SWS, slow wave sleep.
events/h; between-group difference was −11.5 events/h (95% CI −28.3 to 5.3; P=0.18) over 2 years compared to lifestyle intervention (dietary, physical activity and behavioural conventional programme) (15). In a recent post hoc analysis of this RCT, patients who achieved a normal supine AHI (i.e. AHI <5/h) lost significantly more weight than those who had persistently elevated AHI (weight change −23.0 (−21.0 to −31.6)% vs −6.9 (−1.9 to −17.4%), P=0.001) (19). Other studies also showed significant improvements in the AHI and a high proportion of OSA resolution following sleeve gastrectomy and gastric bypass (16, 17). A meta-analysis confirmed the positive impact of bariatric surgery on OSA severity, by showing a significant reduction of AHI post surgery (by 38.2 events/h, 95% CI: 31.9–44.4) (20). A more recent systematic review and meta-analysis by Wong et al. showed that bariatric surgery was associated with a reduction in the AHI (WMD −25.1 events/h (95% CI −29.9, −20.2)); with the pooled mean pre- and post-surgery AHI of 39.3 ± 15.1 and 12.5 ± 5.6 events/h respectively; however, OSA persisted in most patients and there was high between-studies heterogeneity mostly due to baseline AHIO and duration of follow-up (21). Hence, RCTs remain needed to address the impact of bariatric surgery on OSA, although these might be challenging to conduct. In another RCT, liraglutide 3 mg daily combined with lifestyle intervention resulted in greater reductions in weight (−5.7% vs −1.6%, P<0.0001) and AHI (−12.2 vs −6.1 events/h, estimated treatment difference: −6.1 events/h; 95% CI −11.0 to −1.2, P=0.015) compared to lifestyle intervention only over 32 weeks (18). The degree of weight loss correlated significantly with improvements in OSA in this trial (18).

Obesity can affect multiple aspects of OSA pathogenesis, as summarised in Fig. 2 (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36).

The impact of OSA on weight

The impact of OSA on obesity is controversial. One possibility is that OSA could lead to worsening obesity via multiple mechanisms such as increased excessive daytime sleepiness (EDS), sedentary behavior, increased appetite, increased BMI, increased fat mass, reduced muscle mass and activity, and reduced energy expenditure. Obesity can lead to increased upper airway resistance and reduced lung volume resulting in increased work of breathing and reduced oxygen delivery to the brain. In addition, the low lung volume in obesity can lead to hypoxaemia and ventilatory instability in the presence of increased whole body oxygen demand due to obesity (high loop gain) (28).

Figure 2

OSA and obesity interplay. (A) The potential mechanisms linking obesity to obstructive sleep apnoea. (B) The potential impact of obstructive sleep apnoea and its treatment on weight and the underlying mechanisms. Pink boxes are the mechanisms of OSA that might lead to weight gain and the blue boxes are the mechanisms of possible weight loss in OSA. UA, upper airways; TNFA, tumour necrosis factor-alpha; IL6, interleukin-6; CNS, central nervous system; EDS, excessive daytime sleepiness; CPAP, continuous positive airway pressure. Obesity can lead to increased UA collapsibility via increased parapharyngeal fat deposition, UA narrowing, intramuscular fatty deposits leading to reduced UA muscles activity and increased UA muscle fatigability and reduced lung volume resulting in reduced tracheal caudal traction (19, 20, 21, 22, 23, 24, 25, 26, 27). In addition, the low lung volume in obesity can lead to hypoxaemia and ventilatory instability in the presence of increased whole body oxygen demand due to obesity (high loop gain) (28).
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sleepiness (EDS) leading to a reduction in physical activity, sleep disruption leading to changes in hunger and satiety hormones (37, 38, 39) (leptin resistance, increased ghrelin, increased orexin and neuropeptide Y levels), changes to sleep duration and architecture (40, 41, 42, 43, 44). Sleep restriction was associated with increased activation of the brain regions related to emotional response to stimuli and motivation and reward system based on functional MRI, which was similar to what observed following energy deprivation resulting in corrective behaviour of seeking food (45, 46). This is supported by cross-sectional studies showing that the AHI was significantly associated with increased preference of calorie-dense foods independent of the severity of obesity in adolescents and children (47, 48) and that visceral obesity was increased in patients with OSA and short sleep duration (<5 h/night) (OR, 4.40, 95% CI 1.80–10.77), compared to those who slept ≥7 h/night (49). In addition, disruption of sleep architecture (suppression of SWS as happens in OSA) without affecting sleep duration in young healthy men, increased hunger for high-calorie food in the afternoon and evening (50). OSA could also contribute to increased fat mass by activation of the HPA axis and increased cortisol secretion and by hypercapnia-induced adipogenesis (51, 52). However, despite the above-mentioned plausible mechanisms, epidemiological evidence for an impact of OSA on weight longitudinally is lacking. One small (n=53) prospective study of patients with newly diagnosed OSA showed 7.4 ± 1.5 kg weight gain over 12 months, but these patients had also a history of weight gain in the year preceding OSA diagnosis (53), hence quantifying the impact of OSA is difficult without an appropriate control group (Fig. 2B).

Nonetheless, if OSA is a cause of obesity, then it would be expected that OSA treatment will lead to weight loss. However, a systematic review of 3181 patients from 25 RCTs showed that CPAP resulted in a modest but statistically significant increase in BMI and weight compared to control (BMI change: −0.018 ± 0.243 kg/m² for controls vs 0.134 ± 0.273 kg/m² for CPAP; weight change: −0.096 ± 0.718 kg for controls vs 0.417 ± 0.718 kg for CPAP) (54). The mechanisms behind the weight gain after CPAP are not fully elucidated. However, CPAP reduces leptin (satiety hormone), intermittent hypoxia and sympathetic activity leading to reductions in lipolysis and energy expenditure and hence can cause weight gain (55, 56, 57, 58, 59, 60, 61).

Furthermore, it is plausible that OSA can lead to weight loss via increased sympathetic activity leading to increased energy expenditure and lipolysis via lipoprotein lipase inhibition and sympathetic activation (62, 63). The net effects of the above-mentioned opposing mechanisms/impacts of weight gain and weight loss is potentially weight maintenance in patients with OSA. CPAP treatment tilts the balance between these opposing mechanisms towards weight gain by inhibiting sympathetic activity (Fig. 2), but this might be opposed to a certain degree by the impact of CPAP on increasing growth hormone (GH) levels leading to lipolysis (64). The above, however, is only a hypothesis that requires further investigations.

OSA and dysglycaemia

As obesity is a major risk factor for OSA, much of the research in this field has focused on pre-diabetes/T2D. However, it is now increasingly recognised that OSA is common in patients with T1D as well. In this section, we will focus mostly on pre-diabetes/T2D but we will also summarise the evidence regarding T1D.

Epidemiology

In general population studies, OSA has been shown to be associated with various comorbidities, including T2D (9), which is not surprising since obesity is a common risk factor for OSA and T2D (7, 65). Several cross-sectional studies showed a high prevalence of OSA (mild: 5 ≤ AHI < 15; moderate: 15 ≤ AHI < 30; severe: AHI ≥ 30) in patients with T2D (8.5–86%, 23.8–70% moderate-to-severe OSA), and a high prevalence of T2D in patients with OSA (15–30%) (7, 66). This variation in prevalence estimates is due to different diagnostic methods and criteria used to define OSA and differences in study populations (67, 68, 69, 70, 71).

Longitudinal studies have also shown that OSA is an independent risk factor for the development of T2D. A recent meta-analysis of eight studies (63,647 participants) showed that OSA was an independent risk factor for T2D after adjustment for age, sex and BMI (adjusted RR: 1.49, 95% CI: 1.27–1.75), which remained significant even in studies that defined OSA as AHI ≥ 5 (adjusted RR: 1.42; 95% CI 1.02–1.99) (72). A small RCT of 12 weeks in 80 patients with obesity (BMI >45 kg/m² and mostly with metabolic syndrome) suggested that CPAP resulted in improvements in impaired glucose tolerance status compared to no CPAP and that CPAP lowered the 2-h glucose levels following OGTT (73). However, there remains a need for large RCTs of long duration to assess the impact of CPAP, on its own or in combination with lifestyle intervention, on T2D prevention.
OSA and insulin resistance and β-cell function

The impact of OSA on incident T2D is likely to be mediated by the effects of OSA on insulin resistance (IR) and β-cell dysfunction (7). Studies that examined the relationship between OSA and IR had conflicting results, due to variations in the definitions of OSA and IR, but most of the studies showed an association (65). The association between OSA and IR was present in lean men, suggesting that the relationship is not dependant on obesity (74, 75). Variation in EDS might contribute to the variation in the associations between IR and OSA observed in the different studies as Barcelo et al. showed that the association between OSA and IR was only evident in patients with EDS vs without EDS despite being matched for BMI (76). In support of the relationship between OSA and IR, a recent meta-analysis of six RCTs of adults without diabetes showed a favourable effect of CPAP on IR vs no CPAP (mean difference in HOMA-IR: −0.43; 95% CI: −0.75 to −0.11, P=0.008) (77).

The impact of OSA on β-cell function is much less examined in the literature. In one study of patients without diabetes, patients with moderate-to-severe OSA had a lower β-cell function (measured using the disposition index during frequent sampling intravenous glucose tolerance test (IVGTT)) compared to healthy controls; and higher AHI was associated with lower β-cell function despite adjustment for obesity (78). Similar results were found in a more recent study (79) and in another study in patients with T2D (80). Similar to IR, CPAP improved β-cell function in compliant patients with moderate-to-severe OSA without diabetes (uncontrolled trial) (81) or with pre-diabetes (RCT) (82).

Mechanisms: OSA leading to dysglycaemia and T2D

There are several putative mechanisms linking intermittent hypoxia (IH) and sleep fragmentation to IR, β-cell dysfunction and dysglycaemia (33) summarised in Fig. 3.

In rodent models, IH has been shown to increase β-cell death (83) and impair β-cell function (84). Results from experimental studies in healthy adults showed that 5 h of IH (24.3 events/h, average oxygen saturation 90.6%, range 75.4–98%) resulted in blunted, rather than increased, insulin secretion despite reductions in insulin sensitivity (based on IVGTT) (85). Chronic IH can lead to β-cell dysfunction and IR via increased oxidative stress (86), which pancreatic β-cells are less able to handle compared to other tissues (87, 88, 89), and increased inflammation (increased CD8$^+$ cytotoxic T-cells recruitment, shift to M1-proinflammatory macrophages in crown-like structures, IL and TNFA) (90, 91). In addition, chronic IH can increase free fatty acid (FFA) release leading to ectopic fat deposition in the liver and muscle rusting in IR (90). The impacts of chronic IH and oxidative stress on IR could also be mediated by hypoxia-inducible factor (HIF) tissue effects (92). In rodents, 35 days of chronic IH decreased insulin receptor expression and phosphorylation in skeletal muscle and adipose tissue, but not in the liver which was accompanied by upregulation of HIF1α in the liver and downregulation of HIF1α and HIF2α in skeletal muscle (93).

Changes in sleep architecture can also contribute to the effects of OSA on glucose metabolism (94). In an experimental study of young healthy adults, all-night suppression of SWS (without awakening the subjects, changing sleep duration or REM sleep) was achieved via acoustic stimuli of varying intensity and frequency for three nights (94). This resulted in a reduction in insulin sensitivity (by 25%, which is similar to a weight gain of 8–13 kg) without a compensatory increase in insulin release (based on IVGTT) (94). These changes in insulin sensitivity and β-cell function were associated with increased sympathetic activity and in some cases changes in cortisol levels (94, 95). In addition, several other neurohormonal mechanisms are involved in the links between OSA and T2D, which are summarised in Fig. 3 (30, 39, 51, 65, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113).

The impact of dysglycaemia on OSA

While the impact of OSA on glucose metabolism has been widely studied, the impact of T2D and dysglycaemia on OSA has not received much attention. Many cross-sectional studies showed a high prevalence of OSA in patients with T2D as we detailed above, but whether this prevalence is higher than an age- and obesity-matched population without T2D remains unclear. Recently, a population-based study of 151,194 participants with T2D showed a hazard risk of incident OSA 1.53 (95% CI: 1.32–1.77) and further patients treated with insulin had higher risk of OSA, especially if they were women (1.43; 95% CI: 1.11–1.83) (114). In addition, the incidence and natural history of OSA in patients with T2D are currently unknown. One longitudinal study assessed the relationship between IR and possible OSA prospectively and showed that HOMA-IR was an independent predictor for incident witnessed sleep
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Figure 3

The potential bidirectional relationship and the underlying mechanisms between obstructive sleep apnoea and type 2 diabetes. SWS, slow wave sleep; CB, carotid body; FFA, free fatty acid; ROS, reactive oxygen species; NAFLD, nonalcoholic liver disease; HPA, hypothalamic-pituitary-adrenal axis; T2D, type 2 diabetes. IH and sleep disruption result in increased oxidative stress and inflammation leading to IR an ß-cell dysfunction. In addition, OSA can lead to dysglycaemia via activation of the hypothalamus–pituitary–adrenal (HPA) axis, changes in the growth hormone (GH)/IGF axis, hyperaldosteronism (via hypokalaemia, increased oxidative stress and inflammation), increased ghrelin, increased leptin and reduced adiponectin (40, 48, 90, 91, 92, 93, 94, 95). Interestingly, CPAP treatment can interrupt most of the above-mentioned pathways which might explain the favourable effects of CPAP on IR (96). However, the impact of CPAP on leptin and adiponectin has not been consistent between the different studies (97, 98, 99, 100, 101). Furthermore, patients with OSA (due to recurrent micro arousals, the loss of SWS and the IH (59)) have increased sympathetic activity which can contribute to the increased IR (30, 102). The IH, via oxidative stress and its impact on HIF signalling, results in carotid body chemosensory reflex and hence to increased sympathetic activity (103), that is reversible by CPAP (104, 105). Another mechanism that links OSA to dysglycaemia is the increased risk of nonalcoholic fatty liver disease (NAFLD) and progression to steatosis in those patients, due to ectopic fat accumulation and hepatic inflammation, with subsequent effects on insulin sensitivity (106, 107). A recent meta-analysis of nine cohort studies showed that OSA was a predictor of the development and progression of NAFLD (107). On the other hand, dysglycaemia could lead to OSA. One plausible mechanism in patients with pre-diabetes or diabetes is autonomic neuropathy, which might impact on UA innervation (6), ventilatory drive and central respiratory responses to hypercapnia (109, 110). In addition, T2D is associated with reduced pulmonary volumes and functions compared to healthy individuals which could affect UA stability (111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121) and diffusion capacity for carbon monoxide (112, 113, 122, 123). The impact of T2D on the lungs seems to be related to the severity of hyperglycaemia independently of obesity and smoking (123), which raises the possibility that improvements in glycaemic control might have a favourable impact on OSA. Furthermore, treatment intensification in patients with T2D is often associated with weight gain (124), which could lead to the development or worsening of OSA (10, 125). Other independent predictors of incident witnessed apnoeas such as HOMA-IR, hypertriglyceridaemia and smoking are also common in patients with T2D and thus can have a negative impact on OSA (6, 108).
apnoea (not formally diagnosed OSA) over 6 years (OR: 1.31; 95% CI 1.13–1.51) (115).

Several possible mechanisms make it plausible that dysglycaemia/diabetes can lead to the development or worsening of OSA as summarised in Fig. 3 (7, 11, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132).

**OSA in patients with T2D**

**OSA and glycaemic control in T2D**

Several cross-sectional studies in patients with T2D showed that patients with OSA had worse fasting plasma glucose, glycaemic variability and HbA1c compared to patients without OSA despite adjustment for confounders (difference in HbA1c between patients with and without OSA 0.7–3.7%) (7, 133, 134, 135). In addition, OSA severity is correlated with worse glycaemic measures (7). Interestingly, one study showed that the relationship between AHI and HbA1c was only evident for the AHI during REM sleep and not during NREM sleep (after adjustment for confounders) (136). This raised the possibility that OSA treatment might improve glycaemic parameters in patients with T2D.

Several uncontrolled trials showed that CPAP improved glycaemic variability, postprandial glucose levels and HbA1c over the short term (65, 137). However, three RCTs showed conflicting results. Two of these RCTs showed that CPAP had no impact on HbA1c (138, 139), while another RCT showed that CPAP for 6 months lowered HbA1c by −0.4% (95% CI: −0.7% to −0.04%; P = 0.029) while there was no change in HbA1c in the control group (140). These conflicting results could be due to differences in studies population (β-cell reserve), baseline glycaemic control (for example one of the negative RCTs had a baseline HbA1c of 7.3%, while the RCT that showed positive effects of CPAP had baseline HbA1c of 7.6%) (139) or study duration (3 vs 6 months) (138). There were no significant changes in weight or anthropometrics measures in these RCTs between the CPAP and the control arm to explain the conflicting results. However, an important difference between these RCTs was compliance with CPAP; the positive RCT showed CPAP usage of 5.2 h per night compared to below 4 h/night in the trial by West et al. (138, 140). Longer CPAP duration per night might have an important impact on glycaemic control as REM tends to occur later during sleep and the AHI during REM correlated with HbA1c better than the AHI during NREM (82, 136). Hence, there is still a need for well-designed RCTs of longer CPAP duration to answer the question whether CPAP can (or cannot) improve glycaemic control in patients with T2D.

**OSA and vascular complications in patients with T2D**

Several plausible mechanisms have led to the hypothesis that OSA could lead to the development or progression of macro- and microvascular complications in patients with T2D as shown in Fig. 4 (141, 142, 143, 144, 145, 146).

The relationship between OSA and CVD in patients with T2D has not been studied widely. A retrospective observational study showed that in patients with T2D and newly diagnosed OSA, CPAP for 9–12 months lowered systolic (mean change: −6.81, 95% CI: −9.94 to −3.67) and diastolic (−3.69, −5.53 to −1.85) BP (147). Similar reductions in BP levels were observed after 3 months of CPAP in an RCT in which patients with T2D and OSA were randomised to early (<1 week) or late (1–2 months) CPAP (148). The sleep AHEAD study showed an association between AHI and a history of stroke (adjusted OR: 2.57; 95% CI: 1.03–6.42) but not with coronary artery disease (149). In a longitudinal study in 132 patients with T2D and a normal baseline exercise echocardiography test, OSA predicted incident coronary artery disease (adjusted HR: 2.2; 95% CI: 1.2–3.9; P = 0.01) and heart failure (3.5; 1.4–9.0; P < 0.01) over a median follow-up of 4.9 years (150). In another recent study of 1311 patients who had percutaneous coronary intervention (PCI), OSA was associated with increased risk of major adverse cardiac and cerebrovascular events (MACCEs) over 3 years in patients with diabetes mellitus (adjusted HR: 2.03, 95% CI: 1.10–3.74, P = 0.023) after adjustment for age, sex, ethnicity, BMI and hypertension (151). There is no interventional RCT published regarding the impact of CPAP on CVD in patients with T2D.

OSA has been shown to be associated with diabetes-related microvascular complications including peripheral neuropathy, chronic kidney disease (CKD), retinopathy and autonomic neuropathy (71). Most of these studies were cross-sectional and no interventional studies have been published although several are ongoing.

A recent systematic review of 15 cross-sectional studies concluded that there was no convincing evidence that OSA was associated with diabetic retinopathy (DR), but that there was some evidence to suggest that OSA was associated with greater DR severity (152). The systematic review also suggested that OSA was associated with maculopathy (152). It is plausible that the impact of OSA on DR is more related to disease progression rather
than the development of disease (which is a function of hyperglycaemia) (7). The increased retinal oxygen demands overnight will make the retina particularly vulnerable to the effects of the IH that occur in patients with T2D and OSA. This is supported by a recent longitudinal study in patients with T2D in which OSA was not associated with the development of DR but was associated with progression to pre-proliferative and proliferative DR (153). In this longitudinal study, OSA was associated with sight threatening DR (STDR) (adjusted OR: 2.3; 95% CI: 1.1–4.9; \( P=0.035 \)) and maculopathy (adjusted OR: 2.7, 95% CI: 1.2–5.9, \( P=0.01 \)) at baseline (153). After a median follow-up of 43.0 (IQR: 37.0–51.0) months, patients with OSA were more likely than patients without OSA to develop pre-proliferative/proliferative DR (18.4% vs 6.1%; \( P=0.02 \)), which remained significant after adjustment for potential confounders (adjusted OR: 5.2; 95% CI: 1.2–23.0; \( P=0.03 \)) (153). Interestingly in this study, patients with moderate-to-severe OSA who were compliant with CPAP were significantly less likely to develop pre-proliferative/proliferative DR compared to non-compliant patients (153). This finding was supported by another proof-of-concept study that showed that CPAP treatment \( \geq 2.5 \) h/night CPAP over 6 months in individuals with OSA and significant macular oedema was associated with improvement in visual acuity but without improvement in the oedema (154). Currently, RCTs assessing the impact of CPAP on DR are ongoing.

In a systematic review of two longitudinal and ten cross-sectional studies, there was an association between OSA and CKD in patients with T2D (pooled OR: 1.73, 95% CI: 1.13–2.64) (155). In a longitudinal study in patients with T2D, CKD prevalence was higher in patients with OSA vs without OSA (49.3 vs 23.8%, \( P<0.001 \)), which

Figure 4

(A) Mechanisms relating OSA to cardiovascular disease (A) - Adapted with permission from Jullian-Desayes et al. (145) and microvascular complications (B) - Adapted with permission from Tahrani et al. (131) in patients with type 2 diabetes. CRP, C-reactive protein; IH, intermittent hypoxia; NO, nitric oxide; NOx, total nitrate and nitrite; OSA, obstructive sleep apnoea; PKC, protein kinase C; AGE, advanced glycation end product; PARP, poly ADP ribose polymerase; AR, aldose reductase; GAPDH, glyceraldehyde 3-phosphate dehydrogenase. (A) Obstructive sleep apnoea and its cardiometabolic consequences. IH, oxidative stress and inflammation play a key role in OSA and the development of associated cardiometabolic morbidities. Oxidative stress induces inflammation, while increased proinflammatory cytokines, adhesion molecules and procoagulant activities can exacerbate oxidative stress. This vicious circle leads to cardiovascular morbidity. Sympathetic overactivity and the decrease in NO induced by oxidative stress lead to hypertension. Both hypertension and inflammation promote endothelial dysfunction responsible for atherosclerosis, which in turn can also exacerbate oxidative stress (140). In addition, intrathoracic pressure swings and the increase in transmural pressure gradients over vessel walls could also contribute to the endothelial dysfunction observed in OSA. Recurrent arousals also activate the sympathetic nervous system and thus lead to endothelial dysfunction (140). (B) Both OSA and hyperglycaemia share similar molecular consequences including oxidative stress, PKC activation and AGE production. Our own work has shown that patients with OSA and type 2 diabetes have increased oxidative and nitrosative stress increased PARP activation and impaired microvascular function compared with patients with type 2 diabetes only (141).
remained significant after adjustment for confounders (adjusted OR: 2.64, 95% CI: 1.13–6.16, \( P = 0.02 \)). OSA was also associated with lower eGFR and more micro- and macro-albuminuria (156). After an average follow-up of 2.5 (0.7) years, eGFR was greater in patients with vs without OSA (median: −6.8%; IQR: −16.1 to 2.2 vs −1.6%; 7.7 to 5.3%), \( P = 0.002 \) (156). After adjustment, having OSA (\( B = −3.8, \ P = 0.044 \)) and higher AHI (\( B = −4.6, \ P = 0.02 \)) were predictors of lower study-end eGFR (156).

The relationship between OSA and peripheral neuropathy in patients with T2D was examined in a cross-sectional study, which showed that OSA is associated with peripheral neuropathy based on the Michigan Neuropathy Screening Instrument (MNSI) vs patients without OSA (60 vs 27%, \( P < 0.001 \)), which remained significant after adjustment (OR: 2.82; 95% CI: 1.44–5.52; \( P = 0.003 \)) (143). In addition, OSA was associated with lower intraepidermal nerve fibre density (based on skin biopsies), and a history of foot ulceration in patients with T2D (141). These studies suggest that OSA was associated with both large and small fibre neuropathy in patients with T2D. Cohort studies and RCTs assessing the relationship between OSA and CPAP on diabetes-related neuropathy and its complications are ongoing.

## OSA and T1D

As patients with T1D tend to be lean or leaner than patients with T2D, examining OSA in T1D received much less attention than in T2D (157). However, there is increasing interest in OSA in patients with T1D, particularly that some recent studies suggest that OSA in T1D might be more related to autonomic neuropathy rather than obesity (158). In addition, epidemiological studies suggest that obesity prevalence is increasing in patients with T1D which might further increase their risk of developing OSA (159).

In a systematic review of four studies (\( n = 186 \) patients), the prevalence of OSA (defined as AHI \( \geq 5 \)) was 51.9% among adult patients with T1D, but the 95% CI was wide (31.2–72.6) reflecting the small sample size the variation between studies (160). The prevalence of moderate-to-severe OSA (AHI \( \geq 15 \)) in the same meta-analysis was 16.7% (95% CI: 1.1, 34.5) (160).

Autonomic neuropathy was suggested as one potential mechanism for the high prevalence of OSA in T1D as shown in a cross-sectional study of 199 patients with T1D in which OSA was present in 32% of the patients with normal BMI (161). And another study showed a higher prevalence of OSA in patients with T1D and cardiac autonomic neuropathy compared to patients with T1D but without neuropathy (67 vs 23%) (162). Other factors might contribute to the high prevalence of OSA in children and adolescents with T1D including lower mean lung volumes (FVC, PEF, MMEF) (163, 164) and impaired gas exchange with lower diffusing capacity for carbon monoxide (165). There are similar findings of impaired pulmonary function in adult patients with T1D (166, 167, 168).

The natural history, impact and pathogenesis of OSA in patients with T1D remain poorly explored and large well-designed studies are needed.

## OSA and the renin-angiotensin-aldosterone system (RAAS)

The links between OSA and RAAS activation are potentially bidirectional (Fig. 5). Hyperaldosteronism might also play an important role in the well-established links between OSA and hypertension (particularly resistant hypertension-RH) (Fig. 5) (9, 169, 170, 171, 172, 173).

The pathophysiology of hyperaldosteronism in patients with OSA is mainly attributed to the activation of the RAAS due to cyclical/IH (172). In addition, some studies suggested a higher prevalence of primary aldosteronism (PA) in patients with OSA compared to patients without OSA (173).

A recent meta-analysis has examined the relationship between OSA and RAAS activation (174). The meta-analysis included 14 studies, all but one were case–control studies and they included a relatively small sample size (mostly <100, range: 12–120) (174). The studies generally included middle age men and eight of them included patients with hypertension (174). The meta-analysis found no significant relationship between OSA and plasma renin activity (PRA) (mean difference: 0.17 ng/mL per hour (95% CI: −0.22 to 0.55, \( P = 0.40 \))) or plasma renin concentration (PRC) (mean difference 0.95 ng/mL (95% CI: −0.58 to 2.48, \( P = 0.23 \)) (174). However, angiotensin II levels were significantly higher in patients with OSA compared to those without OSA (mean difference of 3.39 ng/L; 95% CI: 2.00–4.79, \( P < 0.00001 \)) (174). There was a trend towards higher plasma aldosterone concentration (PAC) in patients with OSA vs no OSA (mean difference: 0.95 ng/dL; 95% CI: −0.16 to 2.07, \( P = 0.09 \)) (174). However, when examined in patients with and without hypertension separately, patients with hypertension and OSA had significantly higher PAC vs patients with hypertension but without OSA (mean difference: 1.32 ng/dL; 95% CI: 0.58–2.07, \( P = 0.0005 \)) (174).
The above-mentioned meta-analyses had high heterogeneity, which could be due to variations in the definition of OSA (174). The heterogeneity can also be attributed to the medication used prior to RAAS measurements; however, a meta-regression showed that anti-hypertensives did not affect the relationship between OSA and PAC (174). Supporting the findings of this meta-analysis, another study showing that the AHI correlated significantly with PAC and urinary aldosterone levels ($r = 0.568$, $P = 0.0009$; $r = 0.533$, $P = 0.002$, respectively) in patients with RH and hyperaldosteronism (175).

Several uncontrolled studies in patients with hypertension (mostly RH) showed that CPAP lowered angiotensin II and aldosterone levels (176, 177, 178, 179). One RCT in which 117 patients with RH were randomised to CPAP ($n = 57$) vs no CPAP ($n = 60$) showed that 6 months of CPAP resulted in greater reduction in aldosterone excretion (based on 24 h urine) compared to the control group in the per-protocol analysis (mean difference: $-3.3 \mu g/24h$; 95% CI: $-6.1$ to $-0.4 \mu g/24h$; $P = 0.027$) (180). However, the intention-to-treat analysis showed only a trend ($P = 0.07$). The impact of CPAP on lowering aldosterone was particularly evident in those with uncontrolled hypertension, nondipping in nocturnal BP, not using spironolactone and with patients with worse hypoxia (180). A recent meta-analysis of three observational studies and two RCTs (did not include the above-mentioned RCT) showed that CPAP lowered aldosterone levels compared to no/sham CPAP (mean difference: $-0.236$, 95% CI: $-0.45$ to $-0.02$, $P = 0.034$) (181).

Chronic IH seems to play an important role in the impact of OSA on the RAAS and the mechanistic pathway is shown in Fig. 5 (172, 176, 177, 178, 182, 183, 184, 185). On the other hand, RAAS activation and hyperaldosteronism might lead to or worsen OSA.

**Figure 5**
The potential bidirectional relationship between obstructive sleep apnoea and hyperaldosteronism and the plausible linking mechanisms. IH, intermittent hypoxia; RAAS, renin–angiotensin–aldosterone system; RH, resistant hypertension; PA, primary aldosteronism; MR, mineralocorticoid receptors. In rodent studies, IH promoted angiotensin I and AT1 expression, increased the activation of the carotid body by angiotensin II and resulted in increased renin and aldosterone levels leading to increased BP (159, 169, 170). In addition, oxidative stress has been shown to increase the activation of the mineralocorticoid receptors (MR) in rodent models (171). Whether OSA is associated with renin activations remains to be explored as the current studies show a non-significant trend. The increased risk of OSA in patients with hyperaldosteronism is plausible due to increased sodium and fluid retention resulting in UA oedema, increased UA resistance and collapse (159, 176, 177, 178). This might have been worsened further by oedema due to fluid displacement during recumbency overnight particularly in patients with RH (159, 178).
via multiple mechanisms as detailed in Fig. 5. In a retrospective cohort registry-based study, the risk of developing OSA was higher in patients with hypertension and hyperaldosteronism compared to those without hyperaldosteronism after adjustment for age, sex, BMI, diabetes mellitus and heart failure (adjusted OR: 1.8; 95% CI: 1.3–2.6) (186). Moreover, in a cross-sectional study of patients with RH, spironolactone treatment was associated with lower AHI (187). In another uncontrolled study in patients with RH, spironolactone (25–50 mg daily for 8 weeks) improved OSA severity (based on PSG) (AHI: 39.8 ± 19.5 vs 22.0 ± 6.8 events/h; P < 0.05) (188). A recent systematic review and meta-analysis found three studies (one RCT) and concluded that spironolactone reduced the AHI by a mean of –21.12 (95% CI: –27.47 to –14.77, P < 0.00001) (175). Furthermore, in a small study of 20 patients with PA who had PSGs, having MR antagonists (n = 13) or adrenalectomy (n = 7) resulted in AHI reduction from 22.5 (14.7) to 12.3 (12.1) (P = 0.02) (185). These studies support the notion that hyperaldosteronism could worsen OSA and suggest that aldosterone antagonists can be useful in patients with hypertension or PA and OSA.

Finally, due to the links between OSA and PA the recent guidelines of the Endocrine Society on the management of PA recommend that patients with hypertension and OSA are screened for PA (173). Furthermore, well-designed RCTs assessing the impact of MR antagonists on OSA are needed, particularly that OSA is associated with increased CVD risk and that CPAP compliance is often not optimal.

Although not directly related to RAS activation, it is important to note that patients with OSA can present with hypertension and the clinical and biochemical features of phaeochromocytoma without the presence of a catecholamine secreting tumour (i.e. pseudo-phaeochromocytoma) (110, 189, 190, 191). 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 (110, 189, 190, 191).

**OSA and hypothalamic-pituitary-adrenal (HPA) axis**

Cortisol secretion has a well-described circadian rhythm and is closely related to sleep stages (192, 193). Sleep onset and SWS are associated with a decline in cortisol levels followed by increased cortisol secretion in late sleep (which is consistent with the rise in early morning) (194). On the other hand, cortisol might impact on sleep architecture, for example, HPA axis hyperactivity inhibits SWS and promotes nocturnal awakening (193).

**OSA and HPA axis activation**

The impact of OSA on HPA axis is controversial with conflicting results due to the confounding effects of obesity, the sampling frequency (single time point vs 24-h profile), variability in matching between patients with and without OSA, small sample sizes and short CPAP duration with variability in compliance. Some studies showed no relationship between OSA and the HPA axis, while some even suggested that OSA might inhibit the HPA axis (AHI and ODI correlated negatively with morning cortisol levels: r = –0.444, P = 0.002 and r = –0.381, P = 0.011 respectively) (195, 196, 197, 198). 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 HPA activation in patients with OSA in 6/7 studies (199). However, only two of these studies had plasma cortisol measurements over 24 h, while the rest had single time point measurements (199). The two studies that measured 24-h cortisol profile reported contradicting results as one showed no difference in mean 24-h plasma cortisol between patients with OSA and obese controls (200), while the other showed that OSA was associated with HPA activation compared to obese controls (201).

However, the impact of OSA on HPA axis may not necessarily be consistent over the 24-h period, as the study by Vgontzas et al. showed that mean plasma cortisol levels between 23:00 h and 07:00 h were higher in patients with OSA and obesity vs obese controls, consistent with nocturnal HPA activation when there is IH and disruption of the sleep architecture (201) (Fig. 6). Another important aspect is that the impact of OSA on HPA axis may not be simply 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 vs obese controls, the salivary cortisol inhibition following overnight dexamethasone suppression test (ONDST) was significantly less pronounced in patients with OSA compared to obese controls (196). Interestingly, this deficit was corrected after 3 months of CPAP (196). Another study also showed that ACTH responses to CRH stimulation were higher in patients with OSA compared to obese and lean controls (202).

In the same above-mentioned systematic review, eight uncontrolled studies assessed the impact of CPAP on cortisol levels (blood or salivary) (199). Five studies...
showed no impact (76, 196, 203, 204, 205), while three studies showed that CPAP lowered cortisol levels (blood and salivary) (201, 206, 207). The studies that showed favourable impacts of CPAP measured cortisol more frequently during the 24h compared to the negative studies (199). However, a recent in-laboratory study showed that 8h of CPAP per night did not have any effect on 24-h cortisol profile (208). Nonetheless, this study was over a 1-week period, unlike the studies that showed positive impact of CPAP on cortisol which were over 3-month period. A slightly longer study of 14 days, showed that CPAP can lower morning salivary cortisol in men and women with obesity and OSA (209).

The confounding effects of obesity and gender on the relationship between OSA and HPA axis were addressed in a recent study of nonobese men and postmenopausal women which showed that OSA patients had higher 24-h blood cortisol levels compared to controls, which were lowered after 2 months of CPAP (51).

Overall, while the studies showed conflicting results there is evidence that OSA is associated with HPA activation particularly nocturnally and that CPAP (14 days to 3 months) can lower cortisol 24-h profile rather than cortisol levels at single time points. The effects of OSA on the HPA axis can be mediated via mechanisms related to night awakenings (even when brief), sleep restriction and IH (51, 210, 211, 212, 213, 214, 215, 216) as shown in Fig. 6.

**OSA in patients with Cushing’s syndrome**

Several studies have shown that OSA is common in patients with Cushing’s syndrome (CS) (whether endogenous or exogenous) (217). The prevalence of OSA (based on PSG) was higher in women with active CS (n=35) compared to age-, gender- and BMI-matched controls (n=30) (50% vs 23%, P=0.003) (218). After controlling for BMI and HOMA score, serum cortisol remained independently associated with AHI ($R^2$: 77.8%, $P<0.001$), suggesting that the relationship between CS and OSA are not only related to obesity (218). A recent Taiwanese population-based cohort study showed that patients with CS (n=53) were at increased risk of developing OSA compared to matched controlled (matched for age, sex and comorbidities including obesity, T2D and hypertension) (4.11 vs 1.70 per thousand person/year; HR 2.82, 95% CI: 1.67–4.77), with slightly higher risk in men vs women (219). Interestingly in this study, the survival curves for OSA development starting separating clearly from the first year after the diagnosis of CS (219). Similarly, in patients without OSA (n=17) who had PSG before and after 3 months of prednisolone (10mg daily or more), AHI worsened by 56% compared to controls (with mild OSA but no steroid treatment) (220). This increase in AHI did not correlate with changes in weight and neck circumference suggesting mechanisms other than adiposity responsible for the worsening in AHI (220).

While obesity might play an important role in the relationship between CS and OSA, it is clear from the above-mentioned studies that obesity is not the only factor. In addition to obesity, hyperglycaemia, IR and ectopic fat (in the peritoneum, mediastinum and parapharyngeal spaces) may also play a role in the increased risk of OSA in patients with CS (217, 221). Moreover, hypercortisolism can induce UA myopathy leading to compromised UAs (Fig. 6) (217, 219, 222).

Future studies need to assess the impact of CS treatment on the incidence and severity of OSA and to examine whether the increased OSA risk in patients with CS is lifelong or simply related to the period where CS is active. In addition, endocrinologists, surgeons and anaesthetists need to be aware of the high risk of OSA in patients with CS when considering surgical treatment (both pituitary and adrenal) in order to ensure the safety of the surgical intervention.
**OSA and GH/IGF axis**

Summary of OSA impact on GH/IGF axis as well as the relation of GH excess and deficiency to OSA development or worsening can be found in Fig. 7.

**OSA and the dysregulation of GH/IGF axis**

OSA-associated chronic IH and disruption of sleep architecture can lead to dysregulation of the GH/IGF axis as GH secretion is increased after sleep onset and during SWS (both of which are disrupted in patients with OSA) (223, 224). Overall, studies in rodents and humans suggest that OSA is associated with suppression of basal and stimulated GH and IGF1 levels, which are improved by CPAP (225).

In rodents, IH was shown to cause a recoverable dose-dependent suppression of GH release and GH mRNA expression, possibly due to modulation of somatostatin activity (226). In humans, OSA was shown to be associated with a marked reduction in GH blood levels, which increased following one night of CPAP (64). In addition, fasting IGF1 levels correlated negatively with the ODI in men with OSA, but increased following 3 months of CPAP (195). Sleep disruption also plays a role in the relationship between OSA and the GH/IGF1 axis. In an experimental study of patients with OSA who were examined for one night without CPAP and one night with CPAP, GH plasma levels and secretion rate (bloods were collected every 10 min overnight) were reduced and increased after CPAP treatment; this improvement correlated with the improvement in SWS (227).

In support of the impact of OSA on the GH/IGF axis, a recent RCT in 65 middle-aged men with moderate-to-severe OSA showed that CPAP vs sham CPAP increased IGF1 levels, total and pulsatile GH secretion, mean GH concentration, mass of GH secreted per pulse and pulse frequency after 12 weeks of treatment with further increases in IGF1 levels and a decrease in IGFBP1 levels by week 24 (228). Furthermore, other treatments that can...
improve OSA, such as adenotonsillectomy in children, have also been shown to improve IGF1 and IGFBP3 levels (229).

Obesity is a potential confounder for the relationship between OSA and GH/IGF1 dysregulation as obesity (particularly visceral) is linked to a reduction in GH secretion, IGF1 levels and peripheral GH sensitivity, which can recover with weight loss (230). However, IGF1 levels were lower in patients with OSA compared to the weight-matched control despite that both these groups had lower IGF1 levels compared to the lean control (96).

**OSA and acromegaly**

Many cross-sectional studies showed that OSA is highly prevalent in patients with active acromegaly (45–80%) (231), with an average prevalence of 69% in PSG-based studies (232). Although lowering GH/IGF1 improves OSA, up to 40% (range: 21–58% (231)) of those with controlled acromegaly have persistent OSA that required evaluation and the consideration of CPAP (233, 234). ‘Although clinicians seem to be aware of the links between acromegaly and OSA (as shown by a survey in Italy), only few patients undergo PSG in clinical practice (235).

In addition, OSA contributed to the adverse outcomes of acromegaly, despite that there were no differences in GH or IGF1 levels between patients with OSA + acromegaly vs acromegaly alone (236). The presence of impaired glucose tolerance or T2D was higher in patients with acromegaly and OSA vs acromegaly only (n: 10/17 vs 5/19) (236), although this was not adjusted for obesity. In addition, OSA contributed to IR in patients with acromegaly, which improved by CPAP in a RCT (237). Furthermore, OSA might play an important role in other acromegaly-related comorbidities such as hypertension and heart failure/cardio-myopathy (238).

As a result of the high prevalence of OSA and its impact on acromegaly-related comorbidities, the 2014 Endocrine Society Clinical Practice Guideline for acromegaly recommended evaluating all patients for OSA (234). In addition, the guidelines recommended that patients with severe pharyngeal thickness and OSA should be treated with somatostatin receptor ligands preoperatively to reduce the OSA-related surgical risks (234).

On the other hand, a recent study of 507 patients with OSA showed that ten patients (1.97%) had elevated IGF1 levels, of which nine patients suppressed GH levels on OGTT giving an acromegaly prevalence of 0.2% (1/507) (239). These findings suggest that screening for acromegaly in OSA should not be routinely performed. However, if in addition to OSA, there are other features of acromegaly or acromegaly-associated conditions (such as T2D, debilitating arthritis, carpal tunnel syndrome, hyperhidrosis and hypertension), then measurement of IGF1 levels is recommended as per the Endocrine Society Clinical Practice Guideline for acromegaly (239). Finally, although we have focused here on OSA, central sleep apnoea (SA) can also occur in the context of acromegaly (240), but far less common than OSA (236).

The mechanisms leading to the high prevalence of OSA in patients with acromegaly are summarised in Fig. 7 (231, 234, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254).

**The impact of acromegaly treatment on OSA**

Considering that OSA is driven by the excess of GH/IGF1 in patients with acromegaly, it is not surprising that treating acromegaly can improve OSA, but it is also common for OSA to persist or even worsen after acromegaly is brought under control (234). In a small study of six patients with SA syndrome (obstructive or central with EDS) and acromegaly, trans-sphenoidal adenomectomy resulted in resolution of the SA syndrome in all patients regardless of whether acromegaly was cured or not (255). In another study of 24 patients with acromegaly (20 with OSA) who had remission following trans-sphenoidal surgery, at 1 month post surgery, the tongue area declined while the airway volume increased significantly, accompanied with improved OSA (256). The prevalence of severe OSA was reduced from 45.8 to 28% by 6 months with significant improvements in AHI but the average AHI remained in the moderate OSA range (256). Similar results were observed in patients with acromegaly following treatment with somatostatin analogues (246, 249, 257, 258, 259, 260) and pegvisomant (261, 262).

The above-mentioned studies clearly show that curing acromegaly or significant improvements in GH/IGF1 levels can improve OSA, but many patients with acromegaly have persistent moderate-to-severe OSA that might require CPAP. In fact, OSA might occur in patients with acromegaly following achieving normal IGF1 levels even when OSA was not present at baseline as shown by Chemla *et al.* (OSA cured in 57%, new OSA that was not present at baseline 22%) (263). Similarly, Castellani *et al.* showed that AHI increased in 55.5% of patients with acromegaly after complete/partial biochemical control (either after surgery, radiotherapy and/or medical therapy).
OSA in adults with GH deficiency (GHD)

OSA is much less examined in GHD in comparison to acromegaly. OSA is very common in adults with GHD with a prevalence of 63%, which is mainly due to the increased obesity either due to GHD or hypothalamic obesity as a result of surgical or radiotherapy treatment delivered to the underlying pituitary or hypothalamic pathology (265).

GH replacement and OSA

GH replacement in patients with GHD might improve OSA due to a reduction in adiposity (strong lipolytic properties of GH (266, 267)) or it could worsen OSA if the replacement was excessive. The studies in the literature show a mixed picture. In a small study of five men who received GH replacement (median dose: 2U/day; median serum IGFI: 351 µg/L) for 1–2 years post pituitary surgery GHD showed that 6 months after stopping GH treatment the median obstructive AHI decreased significantly from 4.4 to 0.1 (P=0.03), whereas the central AHI increased from 6.3 to 14.6 (P=0.03), suggesting that GH replacement worsened the OSA but improved central SA (268). However, another study of 19 patients with GHD showed that GH replacement for 6 months had no impact on AHI (pre vs post treatment: 28.2/h vs 28/h), regardless of baseline OSA status (265). Still, in a large observational longitudinal study of GH-treated (n=1988) and -untreated (n=442) patients with GHD showed that after a mean follow-up of 2.3 years the SA incidence was greater in the group that received GH replacement (3.3 vs 0.9%, P<0.05), despite that the GH-treated vs -untreated groups had similar BMI at baseline and the GH-treated group were younger (269). However, the GH-treated group had higher baseline IGFI levels (108±61 vs 90±51 µg/L, P<0.001) and serum IGFBP3 levels (2.4±0.9 vs 2.1±1.0 µg/L, P<0.001) (269). In a 12-month double-blind RCT of 40 men with obesity and dysglycaemia who were randomised to either GH or placebo, GH treatment increased IGFI from 168±72 to 292±117 µg/L, the AHI from 31±20 to 43±25 and the ODI from 18±14 to 29±21 (all P values ≤0.001) (270). Interestingly, GH treatment in this study increased neck transverse diameter, circumference and total cross-sectional area, while reduced abdominal visceral adipose tissue (based on CT) (270).

Hence, more data are required to assess the impact of GH replacement on pre-existing OSA and the development of new OSA. However, GH replacement might result in the development or worsening of pre-existing OSA via increasing IGFI levels or via affecting adipose tissue distribution (increasing neck circumference).

OSA in Prader–Willi syndrome

Children and patients with Prader–Willi syndrome (PWS) are also at high risk of having OSA (prevalence: 1:10,000–25,000 live children), and as a result, screening for OSA in this population has been recommended (271). The high prevalence of OSA in patients with PWS is likely to be multifactorial due to GH deficiency, increased viscosity of UAs secretions, craniofacial abnormalities with small airways, UAs muscles hypotonia and secondary alveolar hypoventilation (obesity and scoliosis causing lung volume restriction) all leading to airway collapsibility (271).

The impact of GH replacement on OSA in children with PWS is debatable. Salvatoni et al. showed that short-term treatment with rhGH (6 weeks) did not worsen the AHI, and there was no difference in AHI between the treatment and control group at baseline or study end (272). Nonetheless, in this study, the AHI increased (i.e. OSA worsened) in 50% of the cases following GH replacement (272). Similar results were shown in another study suggesting that the AHI worsens in a subgroup of patients following GH replacement over the short run (273), which in part could be due to the development of adenotonsillar hyperplasty following GH treatment (273). However, longer term follow-up (2 years) showed that GH replacement did not worsen AHI during the follow-up except in those who worsened shortly after GH initiation (274, 275). As a result, the 2013 consensus guidelines considered untreated severe OSA as an exclusion criteria for rhGH initiation, till the patient is treated with CPAP (276, 277). This is particularly important considering that sudden death early in the course of GH replacement in patients with PWS, associated with sleep-disordered breathing/OSA, have been reported in the literature (278, 279, 280).
OSA and hypotalamic-pituitary-thyroid (HPT) axis

OSA in patients with hypothyroidism

A recent systematic review of one observational and five interventional studies (501 patients in their 4th–5th decade of life) found that 25–50% of patients with overt hypothyroidism (OH) had nocturnal breathing abnormalities (snoring, choking, apnoea periods), which improved with levothyroxine 4 (LT4) treatment (281). In one study, 30% of patients with recently diagnosed OH had evidence of OSA (AHI ≥5 based on PSG) and LT4 improved the AHI (from a median of 14.3 (7.4–33.6) to 2.1 (0.8–4.6)) (282). In addition, in the later study LT4 treatment improved hypoxaemia and sleep architecture (TpO2 sat <90%: 14% (2.2–19.9) vs 0.2% (0–1.7), P < 0.05; SWS%: 18.4 (7.2–25.2) vs 28.2 (15–33.4), P < 0.05) (282). This suggests that hypothyroidism can lead to worsened OSA, which improves with LT4 treatment. However, larger studies including RCTs are needed before confirming this relationship.

There is lack of good-quality data regarding the relationship between OSA and subclinical hypothyroidism (SH); one small observational study (n = 108) showed that 53% of patients with untreated SH had OH (based on PSG) (283). However, these results are likely to represent selection bias as the prevalence of OSA in healthy controls with normal thyroid functions was higher (75%) than that in patients with untreated SH despite that SH patients were heavier and the patients are recruited from the respiratory department (283). Hence, currently we cannot be certain about the relationship between OSA and SH.

Hypothyroidism in patients with OSA

While studies are not consistent, overall, there is no evidence that hypothyroidism is more common in patients with OSA compared to patients without OSA (284, 285). A recent study also supported this conclusion as it showed that the prevalence of raised TSH in 813 patients with severe OSA was 4.7% which is similar to the general population (286). Some studies showed that the prevalence of SH was higher in OSA vs control, but these studies have potential selection bias as the population was recruited from sleep clinics and the control group was younger and leaner (287, 288, 289). Other studies did not show a high prevalence of SH in patients with OSA (290). In a study of 245 euthyroid patients with suspected OSA, the prevalence of Hashimoto’s thyroiditis was 32.2% in patients without OSA vs 46.8% in patients with OSA (based on PSG) (P = 0.03) (291). The prevalence of Hashimoto’s increased with worsening severity of OSA (291).

Mechanisms linking OSA and thyroid disorders

Hypothyroidism can lead to the development or worsening of OSA via multiple mechanisms summarised in Fig. 8 (232, 281, 282, 284, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300).

OSA and non-thyroidal illness syndrome (NTIS)

A recent cross-sectional study showed that patients with moderate-to-severe OSA (n = 125) had a higher prevalence of NTIS (defined as normal TSH and low FT3) compared to controls (n = 60) (10.4 vs 0%), but the control group was lean, and there were more men in the OSA group (301). Within the OSA group, patients with NTIS had worse nocturnal hypoxemia compared to patients without NTIS (301). This suggests that IH could play a role in the high prevalence of NTIS in patients with OSA, possibly via downregulation of deiodinase 1 and enhancing deiodinase 3-inactivating T3 and T4 (302). In addition, oxidative stress and low-grade inflammation, resulting from OSA, can also contribute to the association between OSA and NTIS (303, 304). CPAP for 5 months has been shown to improve FT3 levels in patients with NTIS supporting the notion that OSA might lead to NTIS, but this study was not controlled (301). However, it is important the clinicians take into account the possibility of NTIS when interpreting thyroid function results in patients with OSA.

In summary, SA and thyroid specialists need to have a low threshold to test for thyroid disorders if indicated clinically. In addition, OSA can be associated with NTIS and clinicians interpreting the thyroid function results need to take the presence of OSA into consideration. However, cohort studies with well-matched control groups and RCTs are needed to enable us to understand the complex relationship between OSA and HPT axis and the impact of treating one or the other.

OSA and the hypothalamic–pituitary–gonadal (HPG) axis

The interaction between sex hormones and OSA was initially brought to attention by the consistently reporting a higher prevalence of OSA in men vs women.
Obstructive sleep apnoea

This relationship was further emphasised by several observations including that testosterone replacement in men worsens/increases the risk of having OSA, the prevalence of OSA in postmenopausal women was higher than that in premenopausal women; hormone replacement therapy reduced the risk of OSA in postmenopausal women and oral contraceptives were associated with lowered OSA risk in women with polycystic ovarian syndrome (PCOS) (65, 305).

In men

OSA is associated with hypogonadotropic hypogonadism due to altered gonadotropin synthesis and release (306). In a cross-sectional analysis of a prospective study of healthy older men (n = 1312, ≥65 years old), lower testosterone levels (based on quartiles) were associated with significantly less SWS, higher AHI (based on PSG) and more sleep time spent with O₂ sat <90% after adjustment for age and race (307). However, adjustment for BMI made these associations non-significant (307). Other studies showed that patients with OSA had lower area under the curve and mean levels of LH (24.9 ± 10.2 IU/L vs 43.4 ± 9.5 IU/L, P < 0.005) and testosterone (67.2 ± 11.5 nmol/L vs 113.3 ± 26.8 nmol/L, P = 0.003) compared to healthy controls, but the control group was leaner numerically (308). Similar findings were found in other studies (309, 310, 311).

Testosterone replacement and OSA

Patients receiving testosterone replacement are at increased risk of developing OSA. In a cohort study, 3422 of US military service members, aged 40–64 years, who were free of OSA at baseline and received testosterone replacement, were matched based on age and comorbidities to men who did not receive testosterone treatment (312). The absolute 2-year risk of incident OSA was greater in patients who received testosterone replacement vs those who did not (16.5% (95% CI: 15.1–18.1) vs 12.7% (95% CI: 11.4–14.2), P < 0.001) (312). Interestingly, the increased risk of OSA was greater for those who used injectable vs topical testosterone (312). This is also supported by a small RCT in which healthy ambulatory men aged >60 years were randomised to receive three injections of weekly intramuscular testosterone esters (500, 250 and 250 mg) or matching oil-based placebo and then crossed over to the other treatment after 8-week washout. Testosterone replacement in this RCT resulted in worsening RDI (approximately by seven events per hour), mainly...
during non-REM (NREM) sleep and worsened nocturnal hypoxaemia measures, while placebo had minimal effects on RDI and hypoxia parameters (313). Several other studies suggested a link between testosterone replacement and incident or worsening OSA (314, 315, 316, 317). As a result, the Endocrine Society clinical practice guidelines recommended against the use of testosterone replacement in men with untreated severe OSA (318). It is unclear whether different methods of testosterone replacement have a differential impact on the risk of developing or worsening OSA due to the variations in the pharmacokinetics profiles of these agents.

The effects of testosterone can be time limited as shown in a RCT of 67 men who received hypocaloric diet and were randomised to intramuscular injections of 1000 mg testosterone undecanoate or placebo (319), in which testosterone replacement worsened the ODI by 10.3 events/h (95% CI, 0.8–19.8 events/h; P = 0.03) and on nocturnal hypoxaemia at 7 weeks but not at 18 weeks (319). This time-dependent effects might be as a result of time-dependent changes in hypoxic ventilatory recruitment threshold following testosterone replacement (320).

Mechanisms

Low testosterone in men can lead to loss of muscle mass and increased visceral adiposity, which can contribute to the increased/worsening OSA in men with hypogonadism (321, 322). It is unclear how testosterone replacement leads to OSA, but postulated mechanisms include altered ventilator responses such as increased response to hypoxaemia (leading to CO₂ levels below apnoea threshold), reduced sensitivity to hypercapnia or anabolic effects (leading to UA narrowing) and an effect on the neuromuscular control of UA (323, 324). However, these mechanisms are not well proven with multiple studies showing conflicting results. In one interesting mechanistic study, androgen blockade with flutamide did not influence chemo-responsiveness to hypoxia/hypercapnia (325).

In addition, OSA can impact the HPG axis via several mechanisms including IHH, sleep fragmentation and obesity (306, 310, 326). Testosterone levels peak during REM (fewer REM sleep episodes and REM sleep latency are related to lower testosterone concentrations (323)); hence, the disruption of sleep architecture in OSA (loss of REM) might explain the link between OSA and low testosterone (193).

The impact of OSA treatment on the HPG axis

CPAP effects on the HPG axis in men remains controversial with a limited number of studies in the literature. A meta-analysis in 2014 found only two RCTs and five observational studies with a total sample size of 232 men showing the paucity of available data (327). In this meta-analysis, an average of 6 months of CPAP treatment had no effects on testosterone levels despite good CPAP compliance (standardised mean difference (SMD) = –0.14, 95% CI: –0.63 to 0.34) (327). CPAP also had no effects on free testosterone or SHBG levels (327).

Summary of the trials assessing the impact of OSA treatment (CPAP and surgical) on HPG axis can be found in Table 1 (195, 205, 328, 329, 330, 331, 332, 333, 334, 335). The two RCTs showed no effect of CPAP on testosterone levels, but the study participants did not have hypogonadism at baseline and the CPAP duration was short. The uncontrolled studies mostly showed no effects of CPAP on testosterone levels except two studies, which showed that CPAP increased testosterone levels (Table 2). In one of these studies, the increase in total testosterone was associated with increased SHBG, which suggests that the impact of free testosterone was rather limited. In the other study, patients had hypogonadism at baseline and CPAP improved testosterone levels along with LH, but the impact on SHBG was not reported (Table 1). Hence, the impact of CPAP on HPG axis in men remains unclear but future trials need to consider the potential difference in response between men with and without hypogonadism and need to ensure adequate CPAP treatment duration and the impact on free testosterone.

It is important to note that CPAP might still have beneficial impacts on scores for sexual and erection function despite the lack of impact of hormonal measurements (332, 333). However, in two RCTs sildenafil was superior to CPAP in regards to ED (336, 337).

In women

OSA impact on the HPG axis in women is less well studied compared to men. Based on animal studies sex hormones can influence breathing not only via androgens but also via the effects of progesterone and oestradiol on CB and the brainstem (338). In addition, lack of progesterone receptor in rodent led to reduced hypoxic ventilator response (339) and lower UA resistance was found in the luteal phase in healthy premenopausal women with the peak in progesterone secretion (340). On the other hand,
Table 1  Non-randomised trials examining the effects of OSA treatment (CPAP/surgery) on the hypothalamic–pituitary–gonadal (HPG) axis (229, 239, 350, 351, 352, 353, 354, 355, 356, 357). Data are presented as mean or mean ± S.D.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention group</th>
<th>OSA severity (AHI baseline)</th>
<th>CPAP duration (months)</th>
<th>HG at baseline</th>
<th>LH (IU/L)</th>
<th>Total testosterone (nmol/L)</th>
<th>Free testosterone (nmol/L)</th>
<th>SHBG (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
<td>Pre-CPAP</td>
<td>Post-CPAP</td>
<td>Pre-CPAP</td>
<td>Post-CPAP</td>
</tr>
<tr>
<td>(195)</td>
<td>43</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>No</td>
<td>NA</td>
<td>1.2 ± 1.1</td>
<td>3.0 ± 0.47</td>
</tr>
<tr>
<td>(328)</td>
<td>16</td>
<td>51.3</td>
<td>32</td>
<td>7</td>
<td>No</td>
<td>NA</td>
<td>1.8 ± 1.9</td>
<td>4.0 ± 1.7</td>
</tr>
<tr>
<td>(329)</td>
<td>5</td>
<td>49.5</td>
<td>31.7</td>
<td>9</td>
<td>Yes</td>
<td>2.1 ± 0.8</td>
<td>2.6 ± 0.2</td>
<td>2.6 ± 1.1*</td>
</tr>
<tr>
<td>(330)</td>
<td>67</td>
<td>56.2</td>
<td>33.7</td>
<td>6</td>
<td>No</td>
<td>NA</td>
<td>7.4 ± 7.45</td>
<td>20.1 ± 7.32</td>
</tr>
<tr>
<td>(331)</td>
<td>27</td>
<td>65.4</td>
<td>32</td>
<td>3</td>
<td>No</td>
<td>NA</td>
<td>12.7 ± 4.5</td>
<td>11.9 ± 3.5</td>
</tr>
<tr>
<td>(333)</td>
<td>53</td>
<td>43.8</td>
<td>28.7</td>
<td>3</td>
<td>No</td>
<td>5.99 ± 2.5</td>
<td>5.82 ± 2.38</td>
<td>13.45 ± 5.48</td>
</tr>
<tr>
<td>(334)</td>
<td>32</td>
<td>47.4</td>
<td>31.3</td>
<td>1</td>
<td>Yes</td>
<td>4.1 ± 1.8</td>
<td>6.3 ± 2.1*</td>
<td>4.5 ± 1.4</td>
</tr>
<tr>
<td>(335)</td>
<td>12</td>
<td>9</td>
<td>NA</td>
<td>3</td>
<td>No</td>
<td>13.31 ± 1.07</td>
<td>16.59 ± 0.72</td>
<td>NA</td>
</tr>
</tbody>
</table>

*aBMI and age-matched; bBMI matched, but were leaner; cBMI matched but were younger; dstatistically significant.

AHI, apnoea–hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; HG, hypogonadism; LH, luteinizing hormone; NA, not applicable; SHBG, sex hormone binding globulin; UPP, uvulopalatopharyngoplasty.

OSA and polycystic ovarian syndrome (PCOS)

OSA is highly prevalent in women with reproductive age OSA has a negative effect on female sex hormones and on sexual function and is associated with pregnancy complications. In a cohort of 53 women (24–72 years old), AHI >10/h was associated with lower morning levels of SHBG and metabolic disturbances. OSA is associated with an increased risk of metabolic syndrome and cardiovascular disease in women. Women with OSA have lower estradiol and androgen levels, and higher LH levels compared to controls. In a study of 26,308 women, OSA was associated with a 1.29-fold increased risk of PCOS, after adjusting for age, BMI, and menopausal status. The impact of CPAP on the HPG axis in women receiving hormone replacement therapy (HRT) was investigated in 344–346). In this review, we did not discuss the impact of OSA on pregnancy.
compared to controls, and the relationship between OSA severity and hyper-androgenaemia were not consistent across the studies (347). This could be due to the low circulating androgen levels in women with PCOS compared to men.

In another meta-analysis from our group comparing women with PCOS and OSA vs women with PCOS only showed that the earlier group had higher BMI (mean difference: 6.01 kg/m\(^2\), 95% CI: 4.69–7.33), waist circumference (MD: 10.93 cm, 95% CI: 8.03–13.83), IR (HOMA-IR: MD=2.23, 95% CI: 1.41–3.06; \(I^2=0\%\)), systolic BP (10.8 mmHg 95% CI: 6.21–15.39), diastolic BP (4.63 mmHg 95% CI: 1.06–8.21), impaired glucose tolerance (2 h plasma glucose on OGTT: MD = 2.23, 95% CI: 0.67–2.11, \(I^2=0\%\)) and worse lipids profile (higher total cholesterol, LDL and triglycerides and lower HDL) compared to the alter group (349). The androgen levels were not different between the two groups but hirsutism was worse in the OSA group (349). However, these studies included were relatively small, at high risk of selection bias, and did not account for important potential confounders such as obesity (349).

Several mechanisms link PCOS to OSA as summarised in Fig. 9 (350).

### OSA and bone metabolism

Although cross-sectional studies assessing the relationship between OSA and bone mass density (BMD) showed conflicting results (351, 352, 353, 354); longitudinal studies showed an increased risk of osteoporosis in patients with OSA (355, 356). In a large retrospective cohort study of 1377 patients with newly diagnosed OSA and 22,655 matched controls (age, sex and index date), the risk of osteoporosis was greater in patients with OSA vs control in both men and women (incidence rate: 2.52/1000 person-years vs 1.00/1000 person-years, adjusted HR: 2.74, 95% CI: 1.69–4.44) over the 6-year follow-up (355). The HR in this study was adjusted for age, gender, diabetes status, obesity, CVD risk factors, CKD, CVD, gout and social demographics.

Consistent with the increased risk of osteoporosis in patients with OSA, several studies suggested that OSA might increase the risk of fractures, although these studies examined conditions that are related to OSA rather than OSA per se. In a study of 2911 men older than 67 years, men who spent \(\geq 10\%\) of their sleep time with \(O_2\) saturations \(<90\%\) had increased risk of incident non-spinal fractures compared to men spent \(<1\%\) of sleep time...
Obstructive sleep apnoea and polycystic ovary syndrome; clinical interactions and underlying pathophysiology. Adapted from Kahal et al. with permission. Sex hormones are thought to play a role in this bidirectional relationship, as in women with PCOS androgens excess along with lower progesterone (as a result of anovulation) can increase UA collapsibility and/or lead to blunted ventilator chemo-responsiveness (322). While, IH and sleep fragmentation can impact HPG axis and can influence GnRH and gonadotropins pulsatility, leading to causing/or worsening PCOS phenotype (322). In addition, IR and dysglycaemia in women with PCOS can contribute to worsening or the development of OSA (322). Obesity is common in both disorders and can contribute to the associations between OSA and PCOS. Other common comorbidities are oxidative stress, endothelial dysfunction and sympathetic activation all of which can lead to a vicious cycle of OSA and PCOS entities (322).

with \( \text{O}_2 \) saturation <90% over 7 years follow-up (adjusted relative hazards: 1.42, 95% CI: 0.94–2.15, \( P=0.047 \)) (357). In the same study, the relative risk of having ≥1 fall was also higher in the group with nocturnal hypoxaemia (relative risk: 1.25, 95% CI: 1.04–1.51) (357). Another longitudinal study that followed up 8101 women aged 69 years or older for 6 years found that self-reported daily napping was associated with increased risk of incident hip fractures compared to women who did not nap daily (age-adjusted HR: 1.29, 95% CI: 1.02–1.65; fully-adjusted HR: 1.33, 95% CI: 0.99–1.78) and similar to the previous study there was an increased risk of falls in women who napped daily (358). In a recent cohort study, women (n=3220) and men (n=2969) aged 40 years and older, severe snoring (a common OSA symptom) was associated with increased risk of fractures over 10-year follow-up in women (adjusted HR: 1.68, 95% CI: 1.16–2.43, \( P=0.006 \)), with similar non-significant trend in men (359).
Consistent with the increased risk of osteoporosis and fractures in patients with OSA, bone resorption markers (such as serum C-terminal telopeptide of type I collagen CTX) has been shown to be higher in patients with OSA compared to controls in men and the AHI was independently associated with urinary CTX independently of age, BMI and other variables (352, 360). Furthermore, CPAP for 3 months lowered the creatinine-adjusted urinary CTX levels significantly (211±107 vs 128±59μg/mmol/creatinine; P<0.01) (360).

Several mechanisms might explain the impact of OSA on bone turnover, bone density and fracture risk summarised in Fig. 10 (361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373).

Summary and conclusion

In this review we have demonstrated that there are multiple bidirectional interactions between OSA and the endocrine system although the observed relationships varied depending on the endocrine system examined. The impact of OSA on the endocrine system was mostly mediated by intermittent hypoxaemia, sympathetic activation, the elevated BP and the increased inflammation and oxidative stress. While the impact of the endocrine system on OSA was mostly mediated via increased upper body adiposity, narrowing of the UAs, weakening of upper airway muscles, changes to chemosensitivity and ventilatory drive as well as autonomic dysfunction.

Our review also shows that there are multiple knowledge gaps in the field at a mechanistic level and also due to the lack of well-designed cohort and interventional studies in many areas. This is further complicated by the difficulty in achieving good compliance with CPAP in clinical studies, the diurnal nature of the endocrine system and the interaction between OSA and other sleep disorders such as short sleep duration and misalignment in the circadian rhythm. In particular, our review found the following need to be explored in future studies due to either no, minimal or inconsistent evidence currently available: the impact of OSA and CPAP on weight, the impact of diabetes treatment on OSA as well as the impact of OSA on diabetes-related outcomes, the impact of PA treatment on OSA, the effects of OSA on the HPA axis and the natural history of OSA and its response to treatment in patients with CS, the long-term impact of GH replacement on OSA as well as central SA, the impact of thyroxine replacement on OSA in patients with hypothyroidism, the relationship between OSA and SH, the impact of long-term testosterone replacement and the different methods of replacement on OSA, the impact of OSA and CPAP in women with PCOS and men with hypogonadism and the impact of CPAP on bone metabolism.

Finally, clinicians treating patients with endocrine conditions should not assume that OSA would recover by curing the underlying endocrine disorder (such as Cushing’s, acromegaly or hypothyroidism) and that OSA status need to be clarified by formal testing following the successful treatment of the endocrine condition. Furthermore, clinicians, surgeons and anaesthetists involved in the treatment of the endocrine conditions that are associated with OSA need to be aware of this association and treat the OSA in order to improve the safety of the general anaesthesia and surgical procedures.

Supplementary data
This is linked to the online version of the paper at https://doi.org/10.1530/EJE-18-0411.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Obstructive sleep apnoea

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Obstructive sleep apnoea is a common sleep disorder characterized by repeated episodes of upper airway obstruction during sleep. These episodes are associated with decreased airflow, increased respiratory effort, and intermittent hypoxia, which can lead to sleep fragmentation, fatigue, and increased risk of cardiovascular disease.

The pathophysiology of obstructive sleep apnoea involves a complex interplay of factors, including obesity, increased neck circumference, and genetic predisposition. The condition is often associated with an increased accumulation of abdominal visceral fat and serum leptin levels, which may contribute to the development of insulin resistance and type 2 diabetes.

Several studies have shown that obstructive sleep apnoea is associated with alterations in the hypothalamic-pituitary-adrenal (HPA) axis. These changes include increased cortisol levels, decreased ACTH levels, and blunted cortisol responses to stress. These alterations are thought to be due to chronic activation of the HPA axis in response to repeated episodes of hypoxia and hypercapnia.

Continuous positive airway pressure (CPAP) therapy is the standard treatment for obstructive sleep apnoea, and it has been shown to improve symptoms, reduce the risk of cardiovascular disease, and improve the function of the HPA axis.

In conclusion, obstructive sleep apnoea is a serious condition that requires prompt diagnosis and treatment. Early intervention with CPAP therapy can improve the outcomes of patients with this condition and prevent the development of comorbid conditions.


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