Mechanisms of endocrinology

Lavrentaki, Aikaterini; Ali, Asad; Cooper, Brendan G.; Tahrani, Abd A.

DOI:
10.1530/EJE-18-0411

License:
Other (please specify with Rights Statement)

Document Version
Peer reviewed version

Citation for published version (Harvard):
Lavrentaki, A, Ali, A, Cooper, BG & Tahrani, AA 2019, 'Mechanisms of endocrinology: mechanisms of disease: the endocrinology of obstructive sleep apnoea', *European Journal of Endocrinology* , vol. 180, no. 3, pp. R91-R125. https://doi.org/10.1530/EJE-18-0411

Mechanisms of disease: The endocrinology of obstructive sleep apnoea

Aikaterini Lavrentaki[1], Asad Ali[2], Brendan G Cooper[3,4], Abd A Tahrani[1,5,6]

[1]Institute of Metabolism and Systems Research, University of Birmingham, Birmingham, UK

[2]Department of Respiratory Medicine, University Hospitals of Coventry and Warwickshire NHS Trust

[3]Department of Respiratory Medicine, University Hospitals of Birmingham NHS Foundation Trust, Birmingham UK

[4]Institute of Clinical Sciences, University of Birmingham, Birmingham, UK.

[5]Centre of Endocrinology, Diabetes and Metabolism, Birmingham Health Partners, Birmingham, UK

[6]Department of Endocrinology, University Hospitals of Birmingham NHS Foundation Trust, Birmingham UK

Corresponding author:

Abd Tahrani

Office 12, 4th floor

Institute of Translational Medicine,

Heritage Building,

Queen Elizabeth Hospital

Edgbaston,

Birmingham B15 2TH

UK

E mail: a.a.tahrani@bham.ac.uk

Keywords: OSA, obstructive sleep apnoea, CPAP, hormones, endocrinology, obesity, diabetes mellitus, dysglycaemia, insulin resistance, hyperaldosteronism, cortisol, Cushing's syndrome, growth hormone, acromegaly, goiter, hypothyroidism, hypogonadism, polycystic ovarian syndrome, osteoporosis, fractures.

Formatted: Not Highlight

Abstract

Obstructive sleep apnoea (OSA) is a common disorder that is associated with serious co-morbidities 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 bi-directional 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 bi-directional 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.

Introduction:

Obstructive Sleep Apnoea (OSA) is a common disorder that affects 13-33% of men and 6-19% of women[1]. OSA is characterized 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]) **(see online supplement)**[3-6]. 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]) **(Figure 1 & online supplement)** [3, 5, 7].

The interactions between OSA and the endocrine system have attracted much attention and they often can be bi-directional, 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 online supplement.

OSA & Obesity Interplay

Obesity is a major risk factor for the development of OSA[9-11], 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].

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

Field Code Changed

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 6-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 life-style interventions, pharmacotherapy, or bariatric surgery as has been shown by several studies among them and randomized controlled trials (RCTs)[14-18].

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 events/hour; between-group difference was -11.5 events/h 95% CI -28.3 to 5.3; P = 0.18) over 2 years compared to life-style intervention (dietary, physical activity and behavioral conventional program)[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/hour, 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 3mg 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 life-style 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 **Figure 2**[22-36] .

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

Field Code Changed

Formatted: Not Highlight

Formatted: Not Highlight

The impact of OSA on weight (Figure 2B)

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) leading to a reduction in physical activity, sleep disruption leading to changes in hunger and satiety hormones[37-39] (leptin resistance, increased ghrelin, increased orexin, and neuropeptide Y levels), changes to sleep duration and architecture[40-44]. 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 behavior 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 ~~OSA could also cause obesity via increased cortisol secretion[51] and hypercapnia induced adipogenesis~~[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.

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/m^2 for controls vs. 0.134±0.273 kg/m^2 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[55-61].

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

Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight

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 **(Figure 2)**, but this might be opposed to a certain degree by the impact of CPAP on increasing GH levels leading to lipolysis[64]. The above, however, is only a hypothesis that requires further investigations. ~~"It is plausible that OSA might have multifaceted effects that can promote weight gain and weight loss resulting in largely opposing effects and when patients receive CPAP then the balance is tilted towards weight gain (**Figure 2**). This is, however, a hypothesis that needs to be examined.~~

Field Code Changed

Formatted: Not Highlight

OSA & 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 recognized 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 studies populations[67-71].

Formatted: Not Highlight

Longitudinal studies have also shown that OSA is an independent risk factor for the development of T2D. A recent meta-analysis of 8 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/m^2 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 6 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 **Figure 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 hours 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 ~~(CIH)~~ 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[87-89], and increased inflammation (increased $CD8^+$ cytotoxic T-cells recruitment, shift to M1-proinflammatory macrophages in crown-like structures, IL and TNF-a)[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 up-regulation of HIF-1α in the liver and down-regulation HIF-1α and HIF-2α in skeletal muscle[93].

Formatted: Not Highlight

Formatted: Not Highlight

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 invovled in the links between OSA and T2D, which are summarised in **Figure 3** [30,39, 51, 65, 96-113].

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 apneas (not formally diagnosed OSA) over 6 years (OR: 1.31; 95%CI1.13-1.51)[115].

Several possible mechanisms make it plausible that dysglycaemia/diabetes can lead to the development or worsening of OSA as summarized in **Figure 3** [7, 11, 115-132].

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 to 3.7%)[7, 133-135]. 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.

Formatted: Not Highlight

Field Code Changed

Formatted: Not Highlight

Formatted: Not Highlight

Several uncontrolled trials showed that CPAP improved glycaemic variability, postprandial glucose levels and HbA1c over the short-term[65, 137]. However, 3 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 glycemic 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 hours per night compared to below 4 hours/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 tend 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.

Formatted: Not Highlight

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 micro- vascular complications in patients with T2D as shown in **Figure 4** [141-146].

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 (MACCE) 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 ≥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 2 longitudinal and 10 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 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 decline 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 intra-epidermal nerve fibre density (based on skin biopsies), and a history of foot ulceration in patients withT2D[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 4 studies (n= 186 patients), the prevalence of OSA (defined as AHI≥ 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 ≥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[166-168]. The natural history, impact, and pathogenesis of OSA in patients with T1D remain poorly explored and large well-designed studies are needed.

Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight

OSA & the Renin-Angiotensin-Aldosterone System (RAAS)

The links between OSA and RAAS activation are potentially bi-directional **(Figure 5)**. Hyperaldosteronism might also play an important role in the well-established links between OSA and hypertension (particularly resistant hypertension-RH) **(Figure 5)**[9, 169-173].

The pathophysiology of hyperaldosteronism in patients with OSA is mainly attributed to the activation of the RAAS due to cyclical/intermittent hypoxia[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 to 120) [174]. The studies generally included middle age men and 8 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 to 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 to 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[176-179]. 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 µg/24 h; 95% CI -6.1 to -0.4 µg/24 h; 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, non-dipping in nocturnal BP, not using spironolactone, and with patients with worse hypoxia[180]. A recent meta-analysis of 3 observational studies and 2 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 **Figure 5** [172,182-185,176-178].

On the other hand, RAAS activation and hyperaldosteronism might lead to or worsen OSA via multiple mechanisms as detailed in **Figure 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 (25-50mg 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 3 studies (1 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, 189-191]. 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, 189-191].

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

OSA & 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-hours 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) [195-198]. 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 2 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 23:00h and 7:00h were higher in patients with OSA and obesity vs. obese controls, consistent with nocturnal HPA activation when there is intermittent hypoxia and disruption of the sleep architecture[201]**(Figure 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 wasn't 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, 8 uncontrolled studies assessed the impact of CPAP on cortisol levels (blood or salivary)[199]. Five studies showed no impact[76, 196, 203-205], while 3 studies showed that CPAP lowered cortisol levels (blood and salivary)[201, 206, 207]. The studies that showed favourable impacts of CPA measured cortisol more frequently during the 24 hours compared to the negative studies[199]. However, a recent in-laboratory study showed that 8 hours 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 months 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 non-obese men and postmenopausal women which showed that OSA patients had higher 24h 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 intermittent hypoxia[51, 210-216] as shown in **Figure 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 **(Figure 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 anesthetists 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.

Formatted: Not Highlight

Formatted: Not Highlight

OSA & Growth Hormone (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 **Figure 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 IGF-1 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 IGF-1 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/IGF-1 axis. In an experimental study of patients with OSA who were examined for 1 night without CPAP and 1 night with CPAP, GH plasma levels and secretion rate (bloods were collected every 10 minutes over night) 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 IGF-1 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 IGF-1 levels and a decrease in IGFBP-1 levels by week

24[228]. Furthermore, other treatments that can improve OSA, such as adenotonsilectomy in children, have also been shown to improve IGF-1 and IGFBP-3 levels[229].

Obesity is a potential confounder for the relationship between OSA and GH/IGF-1 dysregulation as obesity (particularly visceral) is linked to a reduction in GH secretion, IGF-1 levels and peripheral GH sensitivity, which can recover with weight loss[230]. However, IGF-1 levels were lower in patients with OSA compared to the weight matched controlled despite that both these groups had lower IGF-1 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/IGF-1 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 IGF-1 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 insulin resistance 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/cardiomyopathy[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 10 patients (1.97%) had elevated IGF-1 levels, of which 9 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 IGF-1 levels is recommended as per the Endocrine Society Clinical Practice Guideline for acromegaly[239]. Finally, although we have focused

Formatted: Not Highlight

Field Code Changed

Formatted: Not Highlight

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 **Figure 7** [231, 234, 240-254] .

The impact of Acromegaly treatment on OSA:

Considering that OSA is driven by the excess of GH/IGF-1 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 6 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, 257-260] and pegvisomant [261, 262].

The above-mentioned studies clearly show that curing acromegaly or significant improvements in GH/IGF-1 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 IGF-1 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)[231]. OSA persistence following acromegaly treatment is probably due to multiple factors including increased BMI and/ or irreversible craniofacial-skeletal deformities/fibrosis[231]. Hence, OSA evaluation is needed post acromegaly treatment regardless of the normalisation of GH/IGF-1 [264].

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].

Formatted: Not Highlight

Field Code Changed

Formatted: Not Highlight

Formatted: Not Highlight

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 5 men who received GH replacement (median dose 2 U/day; median serum IGF-I 351 mcg/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 sleep apnoea 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 IGF-1 levels (108 ± 61 vs. 90 ± 51 mcg/l, p <0.001) and serum IGFBP-3 levels (2.4 ± 0.9 vs. 2.1 ± 1.0 mcg/l, p<.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 IGF-1 from 168±72 to 292±117 mcg/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 is 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 IGF-1 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 upper airways secretions, craniofacial abnormalities with small airways, upper airways muscles hypotonia and secondary alveolar hypoventilation (obesity and scoliosis causing lung volume restriction) all leading to airway collapsibility [271].

Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight

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 worsen in a subgroup of patients following GH replacement over the short run[273]; which in part could be due to the development of adenotonsillar hyperthophy 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 obstructive sleep apnea 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[278-280].

OSA & hypothalamic-pituitary-thyroid (HPT) axis

OSA in patients with hypothyroidism

A recent systematic review of 1 observational and 5 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%c: 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/worsen 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 OSA (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 recruited from the respiratory department [283]. Hence, currently we cannot be certain about the relationship between OSA and SH.

Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Field Code Changed
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Formatted: Not Highlight
Field Code Changed
Formatted: Not Highlight

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[287-289]. 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 summarized in **Figure 8** [232, 281, 282, 284, 291-300].

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 down-regulation of deidodinase 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, sleep apnoea 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 & the Hypothalamic-Pituitary-Gonadal (HPG) axis

The interaction between sex hormones and OSA was initially brought to attention by the consistently reported a higher prevalence of OSA in men vs. women. This relationship was further emphasized 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 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, ≥65years 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 for LH (24.9 ± 10.2 IU/l h *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 [309-311].

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 that 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 mg, 250 mg, 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 7 events per hour), mainly during non-rapid eye movement (NREM) sleep, and worsened nocturnal hyoxaemia 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[314-317]. 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 hyperoxic 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 apnea 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 IH, 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 2 RCTs and 5 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 (standardized 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, 328-335]). The 2 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 2 studies, that showed that CPAP increased testosterone levels (Table 1). In one of these studies, the increase in total testosterone was associated with increased SHBG which suggest 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 estradiol 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, OSA has a negative effect on female sex hormones and on sexual function and is associated with PCOs.

In a cohort of 53 women (24-72 years old), AHI>10/hr was associated with lower morning levels of 17-OH-progesterone, progesterone and estradiol[341]. However, hormone replacement therapy (HRT) in post-menopausal women was associated with lower prevalence of moderate to severe OSA prevalence compared to women not taking HRT and less time spent in oxygen saturations < 90%, particularly in women who received combined estrogen-progesterone vs. estrogen alone [342]. The impact of CPAP on the HPG axis in women remains to be explored in large studies, and since one small uncontrolled study showed no effect[330] RCTs in this area are needed.

Similar to men, OSA has been associated with sexual dysfunction (FSFI score: desire, arousal, lubrication, orgasm, satisfaction, and pain) in pre- and post- menopausal women compared to matched controls [343, 344 345]. Unlike in men, evidence for CPAP impact on sexual dysfunction in women is lacking[346]. In this review we did not discuss the impact of OSA on pregnancy.

OSA & Polycystic Ovarian Syndrome (PCOS)

OSA is highly prevalent in women of reproductive age with PCOS. A recent systematic review and meta-analysis from our group (15 studies, n=568) showed that 36.1% (95% CI: 22.4-51.0) of women

with PCOS had OSA regardless of the PCOS definition used[347]. In addition, OSA prevalence was significantly higher in obese women with PCOS compared to lean (OR: 3.96, 95%CI: 1.29-12.13) and in adult women compared to adolescents, both of which are expected since obesity and age are main risk factors of OSA, and thus PCOS precedes OSA development[347]. However, in this meta-analysis there was significant heterogeneity among studies, most studies came from the USA in women with obesity (class II) and there is a high level of selection bias since controls came from general population while exposed cohorts were recruited from specialised clinics[347]. It is plausible that in some cases the OSA could precede PCOS development as detailed in a recent study showing that 1/3 of adolescent girls with PCOS had previous tonsillar enlargement/ tonsillectomy [348].

It is also interesting that although androgens are considered to impact OSA pathogenesis, contributing to the higher OSA prevalence in women with PCOS, three studies showed that women with PCOS and increased androgens did not have higher prevalence of OSA compared to controls, and the relationship between OSA severity and hyper-androgonaemia 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 hour plasma glucose on OGTT: MD=2.23, 95%: 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 **Figure 9**[350].

OSA & Bone metabolism

Although cross-sectional studies assessing the relationship between OSA and bone mass density (BMD) showed conflicting results[351-354]; 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 22655 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-old, men who spent ≥ 10% of their sleep time with O2 saturations < 90% had increased risk of incident non-spinal fractures compared to men spent < 1% of sleep time with O2 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 years 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±59 µg/mmol/creatinine; p<0.01)[360].

Several mechanisms might explain the impact of OSA on bone turnover, bone density and fractures risk summarized in **Figure 10** [361-373].

Summary and conclusion:

In this review we have demonstrated that there are multiple bi-directional 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 blood pressure and the increased inflammation

Formatted: Not Highlight

and oxidative stress. While the impact of the endocrine system on OSA was mostly mediated via increased upper body adiposity, narrowing of the upper airways, 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 primary aldosteronism 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 Cushing's syndrome, 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 subclinical hypothyroidism, 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 anesthetists 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.

Declaration of interest:

No Conflicts of Interest to Declare

Funding:

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector. But A.A. Tahrani is a NIHR Clinician Scientist receiving funding from the National Institute for Health Research in the UK (CS-2013-13-029; 2013).

Acknowledgment:

A. A. Tahrani is a clinician scientist supported by the National Institute for Health Research in the UK. The views expressed in this publication are those of the author(s) and not necessarily those of the National Health Service, the National Institute for Health Research, or the Department of Health."

Abbreviations:

American Academy of Sleep Medicine (AASM)
Adrenocorticotropic hormone (ACTH)
Advanced Glycation End Product (AGE)
Apnea- Hypopnea index (AHI)
AngII Receptor Type 1 (AT1)
Body Mass Index (BMI)
Blood Pressure (BP)
Bone Mineral Density (BMD)
Bone Turnover Markers (BTMs)
Chronic Kidney Disease (CKD)
C-terminal telopeptide of type I collagen (CTX)
Continuous Positive Airway Pressure (CPAP)
Cushing's Syndrome (CS)
Diabetic Retinopathy (DR)
Excessive Daytime Sleepiness (EDS)
Electroencephalogram (EEG)
Epworth Sleepiness Scale (ESS)
Forced Vital Capacity (FVC)
Forced Expiratory Volume in the first second (FEV1)
Fasting Plasma Glucose (FPG)
Growth hormone (GH)
GH deficiency (GHD)
Hypoxia-Inducible Factor (HIF)
Hormonal Replacement Therapy (HRT)
Homeostatic Model Assessment for Insulin resistance (HOMA-IR)
Intermittent Hypoxia (IH)
Insulin Resistance (IR)
Intravenous Glucose Tolerance Test (IVGTT)
Laparoscopic Adjustable Gastric Banding (LAGB)
Levothyroxine 4 (LT4)
Maximum Mid Expiratory Flow Rate (MMEF)
Mineralocorticoid Receptors (MR)
Non-Alcoholic Fatty Liver Disease (NAFLD)
Non-rapid eye movement sleep (NREM)
Oral glucose Tolerance Test (OGTT)
Overnight Dexamethasone Suppression Test (ONDST)
Oxygen Desaturation Index (ODI)

Obstructive Sleep Apnoea (OSA)
Parathormone (PTH)
Primary Aldosteronism (PA)
Prader-Willi syndrome (PWS)
Poly ADP Ribose Polymerase (PARP)
Peak Expiratory Flow (PEF)
Percutaneous Coronary Intervention (PCI)
Protein Kinase C (PKC)
Progesterone (PRG)
Polysomnography (PSG)
Randomized Controlled trial (RCT)
Reactive Oxygen Species (ROS)
Renin-Angiotensin-Aldosterone System (RAAS)
Respiratory Arousal Threshold (RAT)
Respiratory Disturbance Index (RDI)
Rapid Eye Movement (REM) sleep
Resistant Hypertension (RH)
Sleep Apnoea (SA)
Sex-Hormone Binding Globulin (SHBG
Short Sleep Duration (SSD)
Vital Capacity (VC)
Slow Wave Sleep (SWS)
Type 1 Diabetes (T1D)
Type 2 Diabetes (T2D)
Upper Airway (UA)
Upper Airways (UAs)

References:

1. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS & Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017 **34** 70-81.
2. Chokroverty S, Thomas RJ & Bhatt M. *Atlas of Sleep Medicine E-Book*. Elsevier Health Sciences, 2013.
3. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. *Proc Am Thorac Soc* 2008 **5** 154-160.
4. al. Ee. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009 **5** 263-276.
5. Deegan P & McNicholas W. Pathophysiology of obstructive sleep apnoea. *European Respiratory Journal* 1995 **8** 1161-1178.
6. Horner RL. Pathophysiology of obstructive sleep apnea. *J Cardiopulm Rehabil Prev* 2008 **28** 289-298.
7. Tahrani AA. Obstructive sleep apnoea in diabetes: Does it matter? *Diab Vasc Dis Res* 2017 **14** 454-462.

8. Young T, Palta M, Dempsey J, Peppard PE, Nieto FJ & Hla KM. Burden of sleep apnea: rationale, design, and major findings of the Wisconsin Sleep Cohort study. *Wmj* 2009 **108** 246-249.
9. Young T, Peppard PE & Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002 **165** 1217-1239.
10. Young T, Peppard PE & Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol (1985)* 2005 **99** 1592-1599.
11. Peppard PE, Young T, Palta M, Dempsey J & Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *Jama* 2000 **284** 3015-3021.
12. Tufik S, Santos-Silva R, Taddei JA & Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. *Sleep Med* 2010 **11** 441-446.
13. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D & Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med* 1994 **154** 1705-1711.
14. Schwartz AR, Gold AR, Schubert N & Stryzak A. Effect of Weight Loss on Upper Airway Collapsibility in Obstructive Sleep Apnea1-3. *Am Rev Respir Dis* 1991 **144** 494-498.
15. Dixon JB, Schachter LM, O'Brien PE, Jones K, Grima M, Lambert G, Brown W, Bailey M & Naughton MT. Surgical vs conventional therapy for weight loss treatment of obstructive sleep apnea: a randomized controlled trial. *Jama* 2012 **308** 1142-1149.
16. Sharples AJ, Charalampakis V, Daskalakis M, Tahrani AA & Singhal R. Systematic Review and Meta-Analysis of Outcomes After Revisional Bariatric Surgery Following a Failed Adjustable Gastric Band. *Obes Surg* 2017 **27** 2522-2536.
17. Priyadarshini P, Singh VP, Aggarwal S, Garg H, Sinha S & Guleria R. Impact of bariatric surgery on obstructive sleep apnoea-hypopnea syndrome in morbidly obese patients. *J Minim Access Surg* 2017 **13** 291-295.
18. Blackman A, Foster GD, Zammit G, Rosenberg R, Aronne L, Wadden T, Claudius B, Jensen CB & Mignot E. Effect of liraglutide 3.0 mg in individuals with obesity and moderate or severe obstructive sleep apnea: the SCALE Sleep Apnea randomized clinical trial. *Int J Obes (Lond)* 2016 **40** 1310-1319.
19. Joosten SA, Khoo JK, Edwards BA, Landry SA, Naughton MT, Dixon JB & Hamilton GS. Improvement in Obstructive Sleep Apnea With Weight Loss is Dependent on Body Position During Sleep. *Sleep* 2017 **40** zsx047-zsx047.
20. Greenburg DL, Lettieri CJ & Eliasson AH. Effects of surgical weight loss on measures of obstructive sleep apnea: a meta-analysis. *Am J Med* 2009 **122** 535-542.
21. Wong AM, Barnes HN, Joosten SA, Landry SA, Dabscheck E, Mansfield DR, Dharmage SC, Senaratna CV, Edwards BA & Hamilton GS. The effect of surgical weight loss on obstructive sleep apnoea: A systematic review and meta-analysis. *Sleep Med Rev* 2018.
22. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA & Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995 **152** 1673-1689.
23. Shelton KE, Woodson H, Gay S & Suratt PM. Pharyngeal fat in obstructive sleep apnea. *Am Rev Respir Dis* 1993 **148** 462-466.
24. Horner R, Mohiaddin R, Lowell D, Shea S, Burman E, Longmore D & Guz A. Sites and sizes of fat deposits around the pharynx in obese patients with obstructive sleep apnoea and weight matched controls. *European Respiratory Journal* 1989 **2** 613-622.
25. Wolk R, Shamsuzzaman AS & Somers VK. Obesity, sleep apnea, and hypertension. *Hypertension* 2003 **42** 1067-1074.
26. Watson RR. *Modulation of Sleep by Obesity, Diabetes, Age, and Diet*. ACADEMIC PressINC, 2016.
27. Carrera M, Barbé F, Sauleda J, Tomás M, Gómez C, Santos C & Agustí AGN. Effects of obesity upon genioglossus structure and function in obstructive sleep apnoea. *European Respiratory Journal* 2004 **23** 425-429.

28. Ray CS, Sue DY, Bray G, Hansen JE & Wasserman K. Effects of Obesity on Respiratory Function 1–3. *American Review of Respiratory Disease* 1983 **128** 501-506.
29. Schwartz AR, Patil SP, Laffan AM, Polotsky V, Schneider H & Smith PL. Obesity and obstructive sleep apnea: pathogenic mechanisms and therapeutic approaches. *Proc Am Thorac Soc* 2008 **5** 185-192.
30. Heinzer RC, Stanchina ML, Malhotra A, Fogel RB, Patel SR, Jordan AS, Schory K & White DP. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005 **172** 114-117.
31. Eckert DJ & Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008 **5** 144-153.
32. Polotsky M, Elsayed-Ahmed AS, Pichard L, Harris CC, Smith PL, Schneider H, Kirkness JP, Polotsky V & Schwartz AR. Effects of leptin and obesity on the upper airway function. *Journal of Applied Physiology* 2012 **112** 1637-1643.
33. Dempsey JA, Veasey SC, Morgan BJ & O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010 **90** 47-112.
34. Phipps P, Starritt E, Caterson I & Grunstein R. Association of serum leptin with hypoventilation in human obesity. *Thorax* 2002 **57** 75-76.
35. Carter R & Watenpaugh DE. Obesity and obstructive sleep apnea: Or is it OSA and obesity? *Pathophysiology* 2008 **15** 71-77.
36. Arnardottir ES, Maislin G, Schwab RJ, Staley B, Benediktsdottir B, Olafsson I, Juliusson S, Romer M, Gislason T & Pack AI. The interaction of obstructive sleep apnea and obesity on the inflammatory markers C-reactive protein and interleukin-6: the Icelandic Sleep Apnea Cohort. *Sleep* 2012 **35** 921-932.
37. Phillips BG, Kato M, Narkiewicz K, Choe I & Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000 **279** H234-237.
38. Hanlon EC & Van Cauter E. Quantification of sleep behavior and of its impact on the cross-talk between the brain and peripheral metabolism. *Proceedings of the National Academy of Sciences* 2011 **108** 15609-15616.
39. Shechter A. Obstructive sleep apnea and energy balance regulation: A systematic review. *Sleep Med Rev* 2017 **34** 59-69.
40. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A & Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000 **85** 1151-1158.
41. Quan SF, O'Connor GT, Quan JS, Redline S, Resnick HE, Shahar E, Siscovick D & Sherrill DL. Association of physical activity with sleep-disordered breathing. *Sleep and Breathing* 2007 **11** 149-157.
42. Chasens ER, Sereika SM, Weaver TE & Umlauf MG. Daytime sleepiness, exercise, and physical function in older adults. *J Sleep Res* 2007 **16** 60-65.
43. Chasens ER, Sereika SM, Houze MP & Strollo PJ. Subjective and objective appraisal of activity in adults with obstructive sleep apnea. *Journal of aging research* 2011 **2011**.
44. Cappuccio FP, Taggart FM, Kandala N-B, Currie A, Peile E, Stranges S & Miller MA. Meta-Analysis of Short Sleep Duration and Obesity in Children and Adults. *Sleep* 2008 **31** 619-626.
45. Benedict C, Brooks SJ, O'daly OG, Almèn MS, Morell A, Åberg K, Gingnell M, Schultes B, Hallschmid M & Broman J-E. Acute sleep deprivation enhances the brain's response to hedonic food stimuli: an fMRI study. *The Journal of Clinical Endocrinology & Metabolism* 2012 **97** E443-E447.
46. St-Onge M-P, McReynolds A, Trivedi ZB, Roberts AL, Sy M & Hirsch J. Sleep restriction leads to increased activation of brain regions sensitive to food stimuli–. *The American journal of clinical nutrition* 2012 **95** 818-824.

47. Beebe DW, Miller N, Kirk S, Daniels SR & Amin R. The association between obstructive sleep apnea and dietary choices among obese individuals during middle to late childhood. *Sleep Med* 2011 **12** 797-799.
48. Spruyt K, Capdevila OS, Serpero LD, Kheirandish-Gozal L & Gozal D. Dietary and physical activity patterns in children with obstructive sleep apnea. *The Journal of pediatrics* 2010 **156** 724-730. e723.
49. Kim NH, Lee SK, Eun CR, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Yun C-H & Kim NH. Short sleep duration combined with obstructive sleep apnea is associated with visceral obesity in Korean adults. *Sleep* 2013 **36** 723-729.
50. Beccuti G & Pannain S. Sleep and obesity. *Current opinion in clinical nutrition and metabolic care* 2011 **14** 402.
51. Kritikou I, Basta M, Vgontzas AN, Pejovic S, Fernandez-Mendoza J, Liao D, Bixler EO, Gaines J & Chrousos GP. Sleep apnoea and the hypothalamic-pituitary-adrenal axis in men and women: effects of continuous positive airway pressure. *Eur Respir J* 2016 **47** 531-540.
52. Kikuchi R, Tsuji T, Watanabe O, Yamaguchi K, Furukawa K, Nakamura H & Aoshiba K. Hypercapnia Accelerates Adipogenesis: A Novel Role of High CO2 in Exacerbating Obesity. *Am J Respir Cell Mol Biol* 2017 **57** 570-580.
53. Phillips BG, Hisel TM, Kato M, Pesek CA, Dyken ME, Narkiewicz K & Somers VK. Recent weight gain in patients with newly diagnosed obstructive sleep apnea. *J Hypertens* 1999 **17** 1297-1300.
54. Drager LF, Brunoni AR, Jenner R, Lorenzi-Filho G, Benseñor IM & Lotufo PA. Effects of CPAP on body weight in patients with obstructive sleep apnoea: a meta-analysis of randomised trials. *Thorax* 2015 **70** 258-264.
55. Drager LF, Jun JC & Polotsky VY. Metabolic consequences of intermittent hypoxia: relevance to obstructive sleep apnea. *Best practice & research Clinical endocrinology & metabolism* 2010 **24** 843-851.
56. Tamisier R, Tan CO, Pepin JL, Levy P & Taylor JA. Blood Pressure Increases in OSA due to Maintained Neurovascular Sympathetic Transduction: Impact of CPAP. *Sleep* 2015 **38** 1973-1980.
57. Tentolouris N, Liatis S & Katsilambros N. Sympathetic system activity in obesity and metabolic syndrome. *Ann N Y Acad Sci* 2006 **1083** 129-152.
58. Spraul M, Ravussin E, Fontvieille AM, Rising R, Larson DE & Anderson EA. Reduced sympathetic nervous activity. A potential mechanism predisposing to body weight gain. *J Clin Invest* 1993 **92** 1730-1735.
59. Chopra S, Rathore A, Younas H, Pham LV, Gu C, Beselman A, Kim IY, Wolfe RR, Perin J, Polotsky VY & Jun JC. Obstructive Sleep Apnea Dynamically Increases Nocturnal Plasma Free Fatty Acids, Glucose, and Cortisol During Sleep. *J Clin Endocrinol Metab* 2017 **102** 3172-3181.
60. Henderson LA, Fatouleh RH, Lundblad LC, McKenzie DK & Macefield VG. Effects of 12 Months Continuous Positive Airway Pressure on Sympathetic Activity Related Brainstem Function and Structure in Obstructive Sleep Apnea. *Front Neurosci* 2016 **10** 90.
61. Harsch I, Konturek P, Koebnick C, Kuehnlein P, Fuchs F, Schahin SP, Wiest G, Hahn E, Lohmann T & Ficker J. Leptin and ghrelin levels in patients with obstructive sleep apnoea: effect of CPAP treatment. *European Respiratory Journal* 2003 **22** 251-257.
62. Gu C, Younas H & Jun JC. Sleep apnea: An overlooked cause of lipotoxicity? *Med Hypotheses* 2017 **108** 161-165.
63. Mahat B, Chasse E, Mauger JF & Imbeault P. Effects of acute hypoxia on human adipose tissue lipoprotein lipase activity and lipolysis. *J Transl Med* 2016 **14** 212.
64. Cooper BG, White JE, Ashworth LA, Alberti KG & Gibson GJ. Hormonal and metabolic profiles in subjects with obstructive sleep apnea syndrome and the acute effects of nasal continuous positive airway pressure (CPAP) treatment. *Sleep* 1995 **18** 172-179.

65. Tahrani AA. Diabetes and sleep apnea. *International Textbook of Diabetes Mellitus, Fourth Edition* 2015 **316-336** by John Wiley & Sons, West Sussex, UK.
66. Pamidi S & Tasali E. Obstructive sleep apnea and type 2 diabetes: is there a link? *Front Neurol* 2012 **3** 126.
67. Amin A, Ali A, Altaf QA, Piya MK, Barnett AH, Raymond NT & Tahrani AA. Prevalence and Associations of Obstructive Sleep Apnea in South Asians and White Europeans with Type 2 Diabetes: A Cross-Sectional Study. *J Clin Sleep Med* 2017 **13** 583-589.
68. West SD, Nicoll DJ & Stradling JR. Prevalence of obstructive sleep apnoea in men with type 2 diabetes. *Thorax* 2006 **61** 945-950.
69. Lam DC, Lui MM, Lam JC, Ong LH, Lam KS & Ip MS. Prevalence and recognition of obstructive sleep apnea in Chinese patients with type 2 diabetes mellitus. *Chest* 2010 **138** 1101-1107.
70. Heffner JE, Rozenfeld Y, Kai M, Stephens EA & Brown LK. Prevalence of diagnosed sleep apnea among patients with type 2 diabetes in primary care. *Chest* 2012 **141** 1414-1421.
71. Tahrani AA. Obstructive sleep apnoea: a diabetologist's perspective. *British Journal of Diabetes* 2016 **16** 107-113.
72. Anothaisintawee T, Reutrakul S, Van Cauter E & Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. *Sleep Med Rev* 2016 **30** 11-24.
73. Salord N, Fortuna AM, Monasterio C, Gasa M, Perez A, Bonsignore MR, Vilarrasa N, Montserrat JM & Mayos M. A Randomized Controlled Trial of Continuous Positive Airway Pressure on Glucose Tolerance in Obese Patients with Obstructive Sleep Apnea. *Sleep* 2016 **39** 35-41.
74. Pamidi S, Wroblewski K, Broussard J, Day A, Hanlon EC, Abraham V & Tasali E. Obstructive sleep apnea in young lean men: impact on insulin sensitivity and secretion. *Diabetes Care* 2012 **35** 2384-2389.
75. Lin Q-C, Zhang X-B, Chen G-P, Huang D-Y, Din H-B & Tang A-Z. Obstructive sleep apnea syndrome is associated with some components of metabolic syndrome in nonobese adults. *Sleep and Breathing* 2012 **16** 571-578.
76. Barcelo A, Barbe F, de la Pena M, Martinez P, Soriano JB, Pierola J & Agusti AG. Insulin resistance and daytime sleepiness in patients with sleep apnoea. *Thorax* 2008 **63** 946-950.
77. Iftikhar IH, Hoyos CM, Phillips CL & Magalang UJ. Meta-analyses of the Association of Sleep Apnea with Insulin Resistance, and the Effects of CPAP on HOMA-IR, Adiponectin, and Visceral Adipose Fat. *J Clin Sleep Med* 2015 **11** 475-485.
78. Punjabi NM & Beamer BA. Alterations in glucose disposal in sleep-disordered breathing. *Am J Respir Crit Care Med* 2009 **179** 235-240.
79. Gu CJ, Li M, Li QY, Li N, Shi GC & Wan HY. Obstructive sleep apnea is associated with impaired glucose metabolism in Han Chinese subjects. *Chin Med J (Engl)* 2013 **126** 5-10.
80. Hermans MP, Ahn SA, Mahadeb YP & Rousseau MF. Sleep apnoea syndrome and 10-year cardiovascular risk in females with type 2 diabetes: relationship with insulin secretion and insulin resistance. *Diabetes/metabolism research and reviews* 2013 **29** 227-234.
81. Çuhadaroğlu Ç, Utkusavaş A, Öztürk L, Salman S & Ece T. Effects of nasal CPAP treatment on insulin resistance, lipid profile, and plasma leptin in sleep apnea. *Lung* 2009 **187** 75-81.
82. Pamidi S, Wroblewski K, Stepien M, Sharif-Sidi K, Kilkus J, Whitmore H & Tasali E. Eight Hours of Nightly Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea Improves Glucose Metabolism in Patients with Prediabetes. A Randomized Controlled Trial. *Am J Respir Crit Care Med* 2015 **192** 96-105.
83. Xu J, Long YS, Gozal D & Epstein PN. Beta-cell death and proliferation after intermittent hypoxia: role of oxidative stress. *Free Radic Biol Med* 2009 **46** 783-790.
84. Wang N, Khan SA, Prabhakar NR & Nanduri J. Impairment of pancreatic beta-cell function by chronic intermittent hypoxia. *Exp Physiol* 2013 **98** 1376-1385.

85. Louis M & Punjabi NM. Effects of acute intermittent hypoxia on glucose metabolism in awake healthy volunteers. *Journal of Applied Physiology* 2009 **106** 1538-1544.
86. Lavie L. Oxidative stress—a unifying paradigm in obstructive sleep apnea and comorbidities. *Progress in cardiovascular diseases* 2009 **51** 303-312.
87. Welsh N, Margulis B, Borg L, Wiklund HJ, Saldeen J & FlodstrÃ M. Differences in the expression of heat-shock proteins and antioxidant enzymes between human and rodent pancreatic islets: implications for the pathogenesis of insulin-dependent diabetes mellitus. *Molecular medicine* 1995 **1** 806.
88. Grankvist K, Marklund SL & Täljedal I. CuZn-superoxide dismutase, Mn-superoxide dismutase, catalase and glutathione peroxidase in pancreatic islets and other tissues in the mouse. *Biochemical Journal* 1981 **199** 393-398.
89. Tasali E & Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. *Proc Am Thorac Soc* 2008 **5** 207-217.
90. Ryan S. Adipose tissue inflammation by intermittent hypoxia: mechanistic link between obstructive sleep apnoea and metabolic dysfunction. *J Physiol* 2017 **595** 2423-2430.
91. Murphy AM, Thomas A, Crinion SJ, Kent BD, Tambuwala MM, Fabre A, Pepin J-L, Roche HM, Arnaud C & Ryan S. Intermittent hypoxia in obstructive sleep apnoea mediates insulin resistance through adipose tissue inflammation. *European Respiratory Journal* 2017 **49** 1601731.
92. Ban J-J, Ruthenborg RJ, Cho KW & Kim J-w. Regulation of obesity and insulin resistance by hypoxia-inducible factors. *Hypoxia* 2014 **2** 171.
93. Sacramento JF, Ribeiro MJ, Rodrigues T, Guarino MP, Diogo LN, Seica R, Monteiro EC, Matafome P & Conde SV. Insulin resistance is associated with tissue-specific regulation of HIF-1alpha and HIF-2alpha during mild chronic intermittent hypoxia. *Respir Physiol Neurobiol* 2016 **228** 30-38.
94. Tasali E, Leproult R, Ehrmann DA & Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proceedings of the National Academy of Sciences* 2008 **105** 1044-1049.
95. Stamatakis KA & Punjabi NM. Effects of sleep fragmentation on glucose metabolism in normal subjects. *Chest* 2010 **137** 95-101.
96. Gianotti L, Pivetti S, Lanfranco F, Tassone F, Navone F, Vittori E, Rossetto R, Gauna C, Destefanis S, Grottoli S, De Giorgi R, Gai V, Ghigo E & Maccario M. Concomitant Impairment of Growth Hormone Secretion and Peripheral Sensitivity in Obese Patients with Obstructive Sleep Apnea Syndrome. *The Journal of Clinical Endocrinology & Metabolism* 2002 **87** 5052-5057.
97. Vestergaard ET, Jessen N, Moller N & Jorgensen JO. Acyl Ghrelin Induces Insulin Resistance Independently of GH, Cortisol, and Free Fatty Acids. *Sci Rep* 2017 **7** 42706.
98. Segal KR, Landt M & Klein S. Relationship Between Insulin Sensitivity and Plasma Leptin Concentration in Lean and Obese Men. *Diabetes* 1996 **45** 988-991.
99. Lam JC, Xu A, Tam S, Khong PI, Yao TJ, Lam DC, Lai AY, Lam B, Lam KS & Mary SM. Hypoadiponectinemia is related to sympathetic activation and severity of obstructive sleep apnea. *Sleep* 2008 **31** 1721-1727.
100. Frankenberg ADV, Reis AF & Gerchman F. Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review. *Arch Endocrinol Metab* 2017 **61** 614-622.
101. Luther JM. Effects of aldosterone on insulin sensitivity and secretion. *Steroids* 2014 **91** 54-60.
102. Chen X, Niu X, Xiao Y, Dong J, Lu M & Kong W. Effect of continuous positive airway pressure on leptin levels in patients with obstructive sleep apnea: a meta-analysis. *Otolaryngol Head Neck Surg* 2015 **152** 610-618.
103. Hobzova M, Salzman R, Stejskal D, Zapletalova J & Kolek V. Serum adiponectin level in obstructive sleep apnea: Relation of adiponectin to obesity and long-term continuous positive airway pressure therapy. *Adv Med Sci* 2016 **61** 130-134.

104. Ng SS, Liu EK, Ma RC, Chan TO, To KW, Chan KK, Ngai J, Yip WH, Ko FW, Wong CK & Hui DS. Effects of CPAP therapy on visceral fat thickness, carotid intima-media thickness and adipokines in patients with obstructive sleep apnoea. *Respirology* 2017 **22** 786-792.
105. Chen LD, Liu JN, Lin L, Wu Z, Li H, Ye YM, Xu QZ & Lin QC. Effect of Continuous Positive Airway Pressure on Adiponectin in Patients with Obstructive Sleep Apnea: A Meta-Analysis. *PLoS ONE* 2015 **10** e0136837.
106. Kritikou I, Basta M, Vgontzas AN, Pejovic S, Liao D, Tsaoussoglou M, Bixler EO, Stefanakis Z & Chrousos GP. Sleep apnoea, sleepiness, inflammation and insulin resistance in middle-aged males and females. *European Respiratory Journal* 2014 **43** 145-155.
107. Hoyos CM, Killick R, Yee BJ, Phillips CL, Grunstein RR & Liu PY. Cardiometabolic changes after continuous positive airway pressure for obstructive sleep apnoea: a randomised sham-controlled study. *Thorax* 2012 **67** 1081-1089.
108. Fisher VL & Tahrani AA. Cardiac autonomic neuropathy in patients with diabetes mellitus: current perspectives. *Diabetes, metabolic syndrome and obesity: targets and therapy* 2017 **10** 419.
109. Semenza GL & Prabhakar NR. The role of hypoxia-inducible factors in carotid body (patho) physiology. *J Physiol* 2018.
110. Kahal H, Tahrani AA, George JT, Barlow IM & Malik MA. Obstructive sleep apnoea; a rare cause of pseudophaeochromocytoma. *Qjm* 2013 **106** 1133-1136.
111. Narkiewicz K & Somers VK. Sympathetic nerve activity in obstructive sleep apnoea. *Acta Physiol Scand* 2003 **177** 385-390.
112. Mishra P, Nugent C, Afendy A, Bai C, Bhatia P, Afendy M, Fang Y, Elariny H, Goodman Z & Younossi ZM. Apnoeic–hypopnoeic episodes during obstructive sleep apnoea are associated with histological nonalcoholic steatohepatitis. *Liver International* 2008 **28** 1080-1086.
113. Jin S, Jiang S & Hu A. Association between obstructive sleep apnea and non-alcoholic fatty liver disease: a systematic review and meta-analysis. *Sleep Breath* 2018.
114. Huang T, Lin BM, Stampfer MJ, Tworoger SS, Hu FB & Redline S. A Population-Based Study of the Bidirectional Association Between Obstructive Sleep Apnea and Type 2 Diabetes in Three Prospective U.S. Cohorts. *Diabetes Care* 2018 **41** 2111-2119.
115. Balkau B, Vol S, Loko S, Andriamboavonjy T, Lantieri O, Gusto G, Meslier N, Racineux JL & Tichet J. High baseline insulin levels associated with 6-year incident observed sleep apnea. *Diabetes Care* 2010 **33** 1044-1049.
116. Evlice A, Ugurel B, Baklan B & Oztura I. Neuropathy and Dysautonomia in Patients with Obstructive Sleep Apnea Syndrome. *Noro Psikiyatr Ars* 2015 **52** 24-28.
117. Tantucci C, Scionti L, Bottini P, Dottorini ML, Puxeddu E, Casucci G & Sorbini CA. Influence of autonomic neuropathy of different severities on the hypercapnic drive to breathing in diabetic patients. *Chest* 1997 **112** 145-153.
118. Vojtkova J, Ciljakova M, Michnova Z & Turcan T. Chronic complications of diabetes mellitus related to the respiratory system. *Pediatr Endocrinol Diabetes Metab* 2012 **18** 112-115.
119. Lecube A, Simó R, Pallayova M, Punjabi NM, López-Cano C, Turino C, Hernández C & Barbé F. Pulmonary Function and Sleep Breathing: Two New Targets for Type 2 Diabetes Care. *Endocr Rev* 2017 **38** 550-573.
120. Dharwadkar AR, Dharwadkar AA, Banu G & Bagali S. Reduction in lung functions in type-2 diabetes in Indian population: correlation with glycemic status. 2011.
121. Klein OL, Aviles-Santa L, Cai J, Collard HR, Kanaya AM, Kaplan RC, Kinney GL, Mendes E, Smith L & Talavera G. Hispanics/Latinos with type 2 diabetes have functional and symptomatic pulmonary impairment mirroring kidney microangiopathy: findings from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL). *Diabetes Care* 2016 **39** 2051-2057.
122. Oda E & Kawai R. A cross-sectional relationship between vital capacity and metabolic syndrome and between vital capacity and diabetes in a sample Japanese population. *Environmental health and preventive medicine* 2009 **14** 284.

123. Kim H-K, Kim C-H, Jung Y, Bae S, Choe J, Park J & Lee K-U. Association of restrictive ventilatory dysfunction with insulin resistance and type 2 diabetes in Koreans. *Experimental and clinical endocrinology & diabetes* 2011 **119** 47-52.
124. Huang H, Guo Q, Li L, Lin S, Lin Y, Gong X, Yao J, Liang J, Lin L & Wen J. Effect of type 2 diabetes mellitus on pulmonary function. *Experimental and clinical endocrinology & diabetes* 2014 **122** 322-326.
125. Lange P, Parner J, Schnohr P & Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. *European Respiratory Journal* 2002 **20** 1406-1412.
126. Walter RE, Beiser A, Givelber RJ, O'connor GT & Gottlieb DJ. Association between glycemic state and lung function: the Framingham Heart Study. *Am J Respir Crit Care Med* 2003 **167** 911-916.
127. Lawlor D, Ebrahim S & Smith GD. Associations of measures of lung function with insulin resistance and type 2 diabetes: findings from the British Women's Heart and Health Study. *Diabetologia* 2004 **47** 195-203.
128. Yeh H-C, Punjabi NM, Wang N-Y, Pankow JS, Duncan BB, Cox CE, Selvin E & Brancati FL. Cross-sectional and prospective study of lung function in adults with type 2 diabetes: the Atherosclerosis Risk in Communities (ARIC) study. *Diabetes Care* 2008 **31** 741-746.
129. van den Borst B, Gosker HR, Zeegers MP & Schols AMWJ. Pulmonary Function in Diabetes. *Chest* **138** 393-406.
130. Klein O, Krishnan J, Glick S & Smith L. Systematic review of the association between lung function and Type 2 diabetes mellitus. *Diabetic Medicine* 2010 **27** 977-987.
131. Tahrani AA, Barnett AH & Bailey CJ. Pharmacology and therapeutic implications of current drugs for type 2 diabetes mellitus. *Nat Rev Endocrinol* 2016 **12** 566-592.
132. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S & Young T. Progression and regression of sleep-disordered breathing with changes in weight: the Sleep Heart Health Study. *Arch Intern Med* 2005 **165** 2408-2413.
133. Papanas N, Steiropoulos P, Nena E, Tzouvelekis A, Maltezos E, Trakada G & Bouros D. HbA1c is associated with severity of obstructive sleep apnea hypopnea syndrome in nondiabetic men. *Vasc Health Risk Manag* 2009 **5** 751-756.
134. Pillai A, Warren G, Gunathilake W & Idris I. Effects of sleep apnea severity on glycemic control in patients with type 2 diabetes prior to continuous positive airway pressure treatment. *Diabetes Technol Ther* 2011 **13** 945-949.
135. Aronsohn RS, Whitmore H, Van Cauter E & Tasali E. Impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. *Am J Respir Crit Care Med* 2010 **181** 507-513.
136. Grimaldi D, Beccuti G, Touma C, Van Cauter E & Mokhlesi B. Association of obstructive sleep apnea in rapid eye movement sleep with reduced glycemic control in type 2 diabetes: therapeutic implications. *Diabetes Care* 2014 **37** 355-363.
137. Guo LX, Zhao X, Pan Q, Sun X, Li H, Wang XX, Zhang LN & Wang Y. Effect of Continuous Positive Airway Pressure Therapy on Glycemic Excursions and Insulin Sensitivity in Patients with Obstructive Sleep Apnea-hypopnea Syndrome and Type 2 Diabetes. *Chin Med J (Engl)* 2015 **128** 2301-2306.
138. West SD, Nicoll DJ, Wallace TM, Matthews DR & Stradling JR. Effect of CPAP on insulin resistance and HbA1c in men with obstructive sleep apnoea and type 2 diabetes. *Thorax* 2007 **62** 969-974.
139. Shaw JE, Punjabi NM, Naughton MT, Willes L, Bergenstal RM, Cistulli PA, Fulcher GR, Richards GN & Zimmet PZ. The Effect of Treatment of Obstructive Sleep Apnea on Glycemic Control in Type 2 Diabetes. *Am J Respir Crit Care Med* 2016 **194** 486-492.
140. Martinez-Ceron E, Barquiel B, Bezos AM, Casitas R, Galera R, Garcia-Benito C, Hernanz A, Alonso-Fernandez A & Garcia-Rio F. Effect of Continuous Positive Airway Pressure on

Glycemic Control in Patients with Obstructive Sleep Apnea and Type 2 Diabetes. A Randomized Clinical Trial. *Am J Respir Crit Care Med* 2016 **194** 476-485.
141. Altaf QA, Ali A, Piya MK, Raymond NT & Tahrani AA. The relationship between obstructive sleep apnea and intra-epidermal nerve fiber density, PARP activation and foot ulceration in patients with type 2 diabetes. *J Diabetes Complications* 2016 **30** 1315-1320.
142. Tahrani AA & Ali A. Oxidative stress, inflammation and endothelial dysfunction: The link between obstructive sleep apnoea and vascular disease in type 2 diabetes. In *Studies in Diabetes*, pp 149-171: Springer, 2014.
143. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Mughal S, Jose B, Piya MK, Barnett AH & Stevens MJ. Obstructive sleep apnea and diabetic neuropathy: a novel association in patients with type 2 diabetes. *Am J Respir Crit Care Med* 2012 **186** 434-441.
144. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005 **54** 1615-1625.
145. Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel A-L, Levy P & Pepin J-L. Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials. *Sleep Med Rev* 2015 **21** 23-38.
146. Tahrani AA & Ali A. Obstructive sleep apnoea and type 2 diabetes. *Eur Endocrinol* 2014 **10** 43-50.
147. Prasad B, Carley DW, Krishnan JA, Weaver TE & Weaver FM. Effects of positive airway pressure treatment on clinical measures of hypertension and type 2 diabetes. *J Clin Sleep Med* 2012 **8** 481-487.
148. Myhill PC, Davis WA, Peters KE, Chubb SP, Hillman D & Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. *The Journal of Clinical Endocrinology & Metabolism* 2012 **97** 4212-4218.
149. Rice TB, Foster GD, Sanders MH, Unruh M, Reboussin D, Kuna ST, Millman R, Zammit G, Wing RR, Wadden TA, Kelley D, Pi-Sunyer X & Newman AB. The relationship between obstructive sleep apnea and self-reported stroke or coronary heart disease in overweight and obese adults with type 2 diabetes mellitus. *Sleep* 2012 **35** 1293-1298.
150. Seicean S, Strohl KP, Seicean A, Gibby C & Marwick TH. Sleep disordered breathing as a risk of cardiac events in subjects with diabetes mellitus and normal exercise echocardiographic findings. *American Journal of Cardiology* 2013 **111** 1214-1220.
151. Koo CY, Drager LF, Sethi R, Ho H-H, Hein T, Jim M-H, Tai B-C, Zhang J-J & Lee C-H. Obstructive Sleep Apnea and Diabetes Independently Add to Cardiovascular Risk After Coronary Revascularization. *Diabetes Care* 2018 **41** e12-e14.
152. Leong WB, Jadhakhan F, Taheri S, Chen YF, Adab P & Thomas GN. Effect of obstructive sleep apnoea on diabetic retinopathy and maculopathy: a systematic review and meta-analysis. *Diabet Med* 2016 **33** 158-168.
153. Altaf QA, Dodson P, Ali A, Raymond NT, Wharton H, Fellows H, Hampshire-Bancroft R, Shah M, Shepherd E, Miah J, Barnett AH & Tahrani AA. Obstructive Sleep Apnea and Retinopathy in Patients with Type 2 Diabetes. A Longitudinal Study. *Am J Respir Crit Care Med* 2017 **196** 892-900.
154. Mason RH, Kiire CA, Groves DC, Lipinski HJ, Jaycock A, Winter BC, Smith L, Bolton A, Rahman NM, Swaminathan R, Chong VN & Stradling JR. Visual improvement following continuous positive airway pressure therapy in diabetic subjects with clinically significant macular oedema and obstructive sleep apnoea: proof of principle study. *Respiration* 2012 **84** 275-282.
155. Leong WB, Jadhakhan F, Taheri S, Thomas GN & Adab P. The Association between Obstructive Sleep Apnea on Diabetic Kidney Disease: A Systematic Review and Meta-Analysis. *Sleep* 2016 **39** 301-308.

156. Tahrani AA, Ali A, Raymond NT, Begum S, Dubb K, Altaf QA, Piya MK, Barnett AH & Stevens MJ. Obstructive sleep apnea and diabetic nephropathy: a cohort study. *Diabetes Care* 2013 **36** 3718-3725.
157. Chiang JL, Kirkman MS, Laffel LM & Peters AL. Type 1 diabetes through the life span: a position statement of the American Diabetes Association. *Diabetes Care* 2014 **37** 2034-2054.
158. Reutrakul S & Mokhlesi B. Obstructive Sleep Apnea and Diabetes: A State of the Art Review. *Chest* 2017 **152** 1070-1086.
159. De Keukelaere M, Fieuws S, Reynaert N, Vandoorne E, Kerckhove KV, Asscherickx W & Casteels K. Evolution of body mass index in children with type 1 diabetes mellitus. *Eur J Pediatr* 2018.
160. Reutrakul S, Thakkinstian A, Anothaisintawee T, Chontong S, Borel A-L, Perfect MM, Janovsky CCPS, Kessler R, Schultes B & Harsch IA. Sleep characteristics in type 1 diabetes and associations with glycemic control: systematic review and meta-analysis. *Sleep Med* 2016 **23** 26-45.
161. Banghoej AM, Nerild HH, Kristensen PL, Pedersen-Bjergaard U, Fleischer J, Jensen AEK, Laub M, Thorsteinsson B & Tarnow L. Obstructive sleep apnoea is frequent in patients with type 1 diabetes. *J Diabetes Complications* 2017 **31** 156-161.
162. Janovsky CCPS, Rolim LCdSP, Sá JRd, Poyares D, Tufik S, Silva AB & Dib SA. Cardiovascular autonomic neuropathy contributes to sleep apnea in young and lean type 1 diabetes mellitus patients. *Front Endocrinol (Lausanne)* 2014 **5** 119.
163. Al-Saadi MM, Meo SA, Al-Drees AM, Mohamed S, Shaikh SA & Al-Rubeaan K. Lung functions in poorly controlled type 1 Saudi diabetic children and adolescents. *Saudi medical journal* 2011 **32** 778-783.
164. Vojtková J, Michnová Z, Turčan T, Ďurdík P, Kryštofová J, Vojarová L, Čiljaková M & Bánovčin P. Lung function tests in children with diabetes mellitus type 1. *Acta Pneumologica et Allergologica Pediatrica* 2010 **13** 5-8.
165. Villa MP, Montesano M, Barreto M, Pagani J, Stegagno M, Multari G & Ronchetti R. Diffusing capacity for carbon monoxide in children with type 1 diabetes. *Diabetologia* 2004 **47** 1931-1935.
166. Stubbe B, Schipf S, Schaper C, Felix SB, Steveling A, Nauck M, Volzke H, Wallaschofski H, Friedrich N, Ewert R, Ittermann T & Glaser S. The Influence of Type 1 Diabetes Mellitus on Pulmonary Function and Exercise Capacity - Results from the Study of Health in Pomerania (SHIP). *Exp Clin Endocrinol Diabetes* 2017 **125** 64-69.
167. Sokolov EI & Demidov Iu I. [Gas exchange function of the lungs in patients with type 1 diabetes mellitus]. *Ter Arkh* 2008 **80** 63-66.
168. Lee MJ, Coast JR, Hempleman SC & Baldi JC. Type 1 Diabetes Duration Decreases Pulmonary Diffusing Capacity during Exercise. *Respiration* 2016 **91** 164-170.
169. Hla KM, Young T, Finn L, Peppard PE, Szklo-Coxe M & Stubbs M. Longitudinal association of sleep-disordered breathing and nondipping of nocturnal blood pressure in the Wisconsin Sleep Cohort Study. *Sleep* 2008 **31** 795-800.
170. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'agostino RB, Newman AB, Lebowitz MD & Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. *Jama* 2000 **283** 1829-1836.
171. Peppard PE, Young T, Palta M & Skatrud J. Prospective study of the association between sleep-disordered breathing and hypertension. *New England Journal of Medicine* 2000 **342** 1378-1384.
172. Ahmad M, Makati D & Akbar S. Review of and Updates on Hypertension in Obstructive Sleep Apnea. *International Journal of Hypertension* 2017 **2017**.
173. Prejbisz A, Kolodziejczyk-Kruk S, Lenders JWM & Januszewicz A. Primary Aldosteronism and Obstructive Sleep Apnea: Is This A Bidirectional Relationship? *Horm Metab Res* 2017 **49** 969-976.

174. Jin Z-N & Wei Y-X. Meta-analysis of effects of obstructive sleep apnea on the renin-angiotensin-aldosterone system. *Journal of geriatric cardiology: JGC* 2016 **13** 333.
175. Zhang W, Zhang J, Wu K, Chen X, Wang Y, Zhou L, Wang H & Chen S. Effect of aldosterone antagonists on obstructive sleep apnea in patients with resistant hypertension: a systematic review and meta-analysis. *Journal of human hypertension* 2017 **31** 855.
176. Zhang X & Li Y. Efficacy of continuous positive airway pressure therapy upon resistant hypertension in patients with obstructive sleep apnea hypopnea syndrome. *Zhonghua yi xue za zhi* 2009 **89** 1811-1814.
177. Lloberes P, Sampol G, Espinel E, Segarra A, Ferrer M, Romero O, Jurado MJ, Ramon MA, Untoria D & Garcia MAM. Effect of 3-month CPAP treatment on blood pressure and serum aldosterone concentration in patients with resistant hypertension. Eur Respiratory Soc: European Respiratory Journal 2013 42: P307, 2013.
178. Lloberes P, Sampol G, Espinel E, Segarra A, Ramon M-A, Romero O, Ferrer R, Martínez-Garcia M-A & Tovar J-L. A randomized controlled study of CPAP effect on plasma aldosterone concentration in patients with resistant hypertension and obstructive sleep apnea. *J Hypertens* 2014 **32** 1650-1657.
179. Møller DS, Lind P, Strunge B & Pedersen EB. Abnormal vasoactive hormones and 24-hour blood pressure in obstructive sleep apnea. *American journal of hypertension* 2003 **16** 274-280.
180. de Souza F, Muxfeldt ES, Margallo V, Cortez AF, Cavalcanti AH & Salles GF. Effects of continuous positive airway pressure treatment on aldosterone excretion in patients with obstructive sleep apnoea and resistant hypertension: A randomized controlled trial. *J Hypertens* 2017 **35** 837-844.
181. Yang S-j, Jiang X-T, Zhang X-B, Yin X-W & Deng W-X. Does continuous positive airway pressure reduce aldosterone levels in patients with obstructive sleep apnea? *Sleep and Breathing* 2016 **20** 921-928.
182. Fung ML, Tipoe GL & Leung PS. Mechanisms of maladaptive responses of peripheral chemoreceptors to intermittent hypoxia in sleep-disordered breathing. *Sheng li xue bao:[Acta physiologica Sinica]* 2014 **66** 23-29.
183. Lam SY, Liu Y, Ng KM, Liong EC, Tipoe GL, Leung PS & Fung ML. Upregulation of a local renin–angiotensin system in the rat carotid body during chronic intermittent hypoxia. *Exp Physiol* 2014 **99** 220-231.
184. Shimosawa T. Salt, the renin–angiotensin–aldosterone system and resistant hypertension. *Hypertension Research* 2013 **36** 657.
185. Wolley M, Pimenta E, Calhoun D, Gordon R, Cowley D & Stowasser M. Treatment of primary aldosteronism is associated with a reduction in the severity of obstructive sleep apnoea. *Journal of human hypertension* 2017 **31** 561.
186. Sim JJ, Yan EH, Liu ILA, Rasgon SA, Kalantar-Zadeh K, Calhoun DA & Derose SF. Positive relationship of sleep apnea to hyperaldosteronism in an ethnically diverse population. *J Hypertens* 2011 **29** 1553-1559.
187. Ke X, Guo W, Peng H, Hu C, Zhang H, Peng C & Wang X. Association of aldosterone excess and apnea-hypopnea index in patients with resistant hypertension. *Scientific Reports* 2017 **7** 45241.
188. Gaddam K, Pimenta E, Thomas SJ, Cofield SS, Oparil S, Harding SM & Calhoun DA. Spironolactone reduces severity of obstructive sleep apnoea in patients with resistant hypertension: a preliminary report. *Journal of human hypertension* 2010 **24** 532.
189. Hoy LJ, Emery M, Wedzicha JA, Davison AG, Chew SL, Monson JP & Metcalfe KA. Obstructive sleep apnea presenting as pseudopheochromocytoma: a case report. *J Clin Endocrinol Metab* 2004 **89** 2033-2038.
190. Cheezum MK & Lettieri CJ. Obstructive sleep apnea presenting as pseudopheochromocytoma. *J Clin Sleep Med* 2010 **6** 190-191.

191. Brainard T. Obstructive sleep apnea and tricyclic antidepressant use presenting as a pseudopheochromocytoma in an active duty sailor: a case report. *Mil Med* 2014 **179** e120-123.
192. Grossman AB. The diagnosis and management of central hypoadrenalism. *The Journal of Clinical Endocrinology & Metabolism* 2010 **95** 4855-4863.
193. Copinschi G & Challet E. Chapter 9 - Endocrine Rhythms, the Sleep-Wake Cycle, and Biological Clocks A2 - Jameson, J. Larry. In *Endocrinology: Adult and Pediatric (Seventh Edition)*, pp 147-173.e149. Eds LJD Groot, DMd Kretser, LC Giudice, AB Grossman, S Melmed, JT Potts & GC Weir. Philadelphia: W.B. Saunders, 2016.
194. Gardner D & Shoback D. *Greenspan's Basic and Clinical Endocrinology, Ninth Edition*. Mcgraw-hill, 2011.
195. Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID & Sullivan CE. Neuroendocrine Dysfunction in Sleep Apnea: Reversal by Continuous Positive Airways Pressure Therapy*. *The Journal of Clinical Endocrinology & Metabolism* 1989 **68** 352-358.
196. Carneiro G, Togeiro SM, Hayashi LF, Ribeiro-Filho FF, Ribeiro AB, Tufik S & Zanella MT. Effect of continuous positive airway pressure therapy on hypothalamic-pituitary-adrenal axis function and 24-h blood pressure profile in obese men with obstructive sleep apnea syndrome. *American Journal of Physiology-Endocrinology and Metabolism* 2008 **295** E380-E384.
197. Karaca Z, Ismailogullari S, Korkmaz S, Cakir I, Aksu M, Baydemir R, Tanriverdi F & Bayram F. Obstructive sleep apnoea syndrome is associated with relative hypocortisolemia and decreased hypothalamo–pituitary–adrenal axis response to 1 and 250 μg ACTH and glucagon stimulation tests. *Sleep Med* 2013 **14** 160-164.
198. Bozic J, Galic T, Supe-Domic D, Ivkovic N, Kurir TT, Valic Z, Lesko J & Dogas Z. Morning cortisol levels and glucose metabolism parameters in moderate and severe obstructive sleep apnea patients. *Endocrine* 2016 **53** 730-739.
199. Tomfohr LM, Edwards KM & Dimsdale JE. Is obstructive sleep apnea associated with cortisol levels? A systematic review of the research evidence. *Sleep Med Rev* 2012 **16** 243-249.
200. Dadoun F, Darmon P, Achard V, Boullu-Ciocca S, Philip-Joet F, Alessi M-C, Rey M, Grino M & Dutour A. Effect of sleep apnea syndrome on the circadian profile of cortisol in obese men. *American Journal of Physiology-Endocrinology and Metabolism* 2007 **293** E466-E474.
201. Vgontzas A, Pejovic S, Zoumakis E, Lin H-M, Bentley C, Bixler E, Sarrigiannidis A, Basta M & Chrousos G. Hypothalamic-pituitary-adrenal axis activity in obese men with and without sleep apnea: effects of continuous positive airway pressure therapy. *The Journal of Clinical Endocrinology & Metabolism* 2007 **92** 4199-4207.
202. Lanfranco F, Gianotti L, Pivetti S, Navone F, Rossetto R, Tassone F, Gai V, Ghigo E & Maccario M. Obese patients with obstructive sleep apnoea syndrome show a peculiar alteration of the corticotroph but not of the thyrotroph and lactotroph function. *Clinical endocrinology* 2004 **60** 41-48.
203. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakamura T, Nakao K & Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999 **100** 706-712.
204. Follenius M, Krieger J, Krauth M, Sforza F & Brandenberger G. Obstructive sleep apnea treatment: peripheral and central effects on plasma renin activity and aldosterone. *Sleep* 1991 **14** 211-217.
205. Meston N, Davies R, Mullins R, Jenkinson C, Wass J & Stradling J. Endocrine effects of nasal continuous positive airway pressure in male patients with obstructive sleep apnoea. *Journal of internal medicine* 2003 **254** 447-454.
206. Schmoller A, Eberhardt F, Jauch-Chara K, Schweiger U, Zabel P, Peters A, Schultes B & Oltmanns KM. Continuous positive airway pressure therapy decreases evening cortisol

concentrations in patients with severe obstructive sleep apnea. *Metabolism-Clinical and Experimental* 2009 **58** 848-853.
207. Henley DE, Russell GM, Douthwaite JA, Wood SA, Buchanan F, Gibson R, Woltersdorf WW, Catterall JR & Lightman SL. Hypothalamic-pituitary-adrenal axis activation in obstructive sleep apnea: the effect of continuous positive airway pressure therapy. *The Journal of Clinical Endocrinology & Metabolism* 2009 **94** 4234-4242.
208. Mokhlesi B, Grimaldi D, Beccuti G & Van Cauter E. Effect of one week of CPAP treatment of obstructive sleep apnoea on 24-hour profiles of glucose, insulin and counter-regulatory hormones in type 2 diabetes. *Diabetes, Obesity and Metabolism* 2017 **19** 452-456.
209. Raff H, Ettema SL, Eastwood DC & Woodson BT. Salivary cortisol in obstructive sleep apnea: the effect of CPAP. *Endocrine* 2011 **40** 137.
210. Yanovski JA & Cutler JG. Glucocorticoid action and the clinical features of Cushing's syndrome. *Endocrinology and Metabolism Clinics of North America* 1994 **23** 487-509.
211. Vgontzas AN, Zoumakis M, Bixler EO, Lin H-M, Prolo P, Vela-Bueno A, Kales A & Chrousos GP. Impaired nighttime sleep in healthy old versus young adults is associated with elevated plasma interleukin-6 and cortisol levels: physiologic and therapeutic implications. *The Journal of Clinical Endocrinology & Metabolism* 2003 **88** 2087-2095.
212. Ekstedt M, Åkerstedt T & Söderström M. Microarousals during sleep are associated with increased levels of lipids, cortisol, and blood pressure. *Psychosomatic medicine* 2004 **66** 925-931.
213. Van Cauter E, Van Coevorden A & Blackman J. Modulation of neuroendocrine release by sleep and circadian rhythmicity. *Advances in neuroendocrine regulation of reproduction* 1990 113-122.
214. Follenius M, Brandenberger G, Bandesapt J, Libert J & Ehrhart J. Nocturnal cortisol release in relation to sleep structure. *Sleep* 1992 **15** 21-27.
215. Pruessner JC, Wolf OT, Hellhammer DH, Buske-Kirschbaum A, Von Auer K, Jobst S, Kaspers F & Kirschbaum C. Free cortisol levels after awakening: a reliable biological marker for the assessment of adrenocortical activity. *Life sciences* 1997 **61** 2539-2549.
216. Caufriez A, Moreno-Reyes R, Leproult R, Vertongen F, Van Cauter E & Copinschi G. Immediate effects of an 8-h advance shift of the rest-activity cycle on 24-h profiles of cortisol. *American Journal of Physiology-Endocrinology and Metabolism* 2002 **282** E1147-E1153.
217. McCarthy V & Caruso A. Sleep apnoea in endocrine diseases Felix Rosenow. *J Sleep Res* 1998 **7** 3-12.
218. Gokosmanoğlu F, Güzel A, Kan EK & Atmaca H. Increased prevalence of obstructive sleep apnea in patients with Cushing's syndrome compared with weight-and age-matched controls. *European Journal of Endocrinology* 2017 **176** 267-272.
219. Wang L-U, Wang T-Y, Bai Y-M, Hsu J-W, Huang K-L, Su T-P, Li C-T, Lin W-C, Chen T-J & Chen M-H. Risk of obstructive sleep apnea among patients with Cushing's syndrome: a nationwide longitudinal study. *Sleep Med* 2017 **36** 44-47.
220. Berger G, Hardak E, Shaham B, Avitan E & Yigla M. Preliminary prospective explanatory observation on the impact of 3-month steroid therapy on the objective measures of sleep-disordered breathing. *Sleep and Breathing* 2012 **16** 549-553.
221. Feelders RA, Pulgar SJ, Kempel A & Pereira AM. MANAGEMENT OF ENDOCRINE DISEASE: The burden of Cushing's disease: clinical and health-related quality of life aspects. *European Journal of Endocrinology* 2012 **167** 311-326.
222. Ceccato F, Bernkopf E & Scaroni C. Sleep apnea syndrome in endocrine clinics. *Journal of endocrinological investigation* 2015 **38** 827-834.
223. Van Cauter E, Latta F, Nedeltcheva A, Spiegel K, Leproult R, Vandenbril C, Weiss R, Mockel J, Legros J-J & Copinschi G. Reciprocal interactions between the GH axis and sleep. *Growth hormone & IGF research* 2004 **14** 10-17.

224. Parker DC, Sassin JF, Mace JW, Gotlin RW & Rossman LG. Human Growth Hormone Release During Sleep: Electroencephalographic Correlation1. *The Journal of Clinical Endocrinology & Metabolism* 1969 **29** 871-874.
225. Lanfranco F, Motta G, Minetto M, Ghigo E & Maccario M. Growth hormone/insulin-like growth factor-I axis in obstructive sleep apnea syndrome: an update. *Journal of endocrinological investigation* 2010 **33** 192-196.
226. Xu NY, Chen XQ, Du JZ, Wang TY & Duan C. Intermittent hypoxia causes a suppressed pituitary growth hormone through somatostatin. *Neuro Endocrinol Lett* 2004 **25** 361-367.
227. Saini J, Krieger J, Brandenberger G, Wittersheim G, Simon C & Follenius M. Continuous positive airway pressure treatment. Effects on growth hormone, insulin and glucose profiles in obstructive sleep apnea patients. *Hormone and Metabolic Research* 1993 **25** 375-381.
228. Hoyos CM, Killick R, Keenan DM, Baxter RC, Veldhuis JD & Liu PY. Continuous positive airway pressure increases pulsatile growth hormone secretion and circulating insulin-like growth factor-1 in a time-dependent manner in men with obstructive sleep apnea: a randomized sham-controlled study. *Sleep* 2014 **37** 733-741.
229. Nieminen P, Löppönen T, Tolonen U, Lanning P, Knip M & Löppönen H. Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics* 2002 **109** e55-e55.
230. Rasmussen MH. Obesity, growth hormone and weight loss. *Mol Cell Endocrinol* 2010 **316** 147-153.
231. Castellani C, Francia G, Dalle Carbonare L, Ferrari M, Viva E, Cerini R, Zaccarella A, Trevisiol L & Davi MV. Morphological study of upper airways and long-term follow-up of obstructive sleep apnea syndrome in acromegalic patients. *Endocrine* 2016 **51** 308-316.
232. Attal P & Chanson P. Endocrine aspects of obstructive sleep apnea. *J Clin Endocrinol Metab* 2010 **95** 483-495.
233. Roemmler J, Gutt B, Fischer R, Vay S, Wiesmeth A, Bidlingmaier M, Schopohl J & Angstwurm M. Elevated incidence of sleep apnoea in acromegaly—correlation to disease activity. *Sleep and Breathing* 2012 **16** 1247-1253.
234. Katznelson L, Laws Jr ER, Melmed S, Molitch ME, Murad MH, Utz A & Wass JA. Acromegaly: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism* 2014 **99** 3933-3951.
235. De Menis E, Giustina A, Colao A, Degli Uberti E, Ghigo E, Minuto F, Bogazzi F, Drigo R, Cattaneo A & Aimaretti G. Assessment of the awareness and management of sleep apnea syndrome in acromegaly. The COM.E.TA (Comorbidities Evaluation and Treatment in Acromegaly) Italian Study Group. *J Endocrinol Invest* 2011 **34** 60-64.
236. Davi MV, Dalle Carbonare L, Giustina A, Ferrari M, Frigo A, Lo Cascio V & Francia G. Sleep apnoea syndrome is highly prevalent in acromegaly and only partially reversible after biochemical control of the disease. *Eur J Endocrinol* 2008 **159** 533-540.
237. Duarte FH, Jallad RS, Amaro AC, Drager LF, Lorenzi-Filho G & Bronstein MD. The impact of sleep apnea treatment on carbohydrate metabolism in patients with acromegaly. *Pituitary* 2013 **16** 341-350.
238. Sharma MD, Nguyen AV, Brown S & Robbins RJ. Cardiovascular Disease in Acromegaly. *Methodist DeBakey cardiovascular journal* 2017 **13** 64.
239. Heinrich DA, Reinholz C, Bauer M, Tufman A, Frohner R, Schopohl J, Bidlingmaier M, Kosilek RP, Reincke M & Schneider HJ. IGF-1-based screening reveals a low prevalence of acromegaly in patients with obstructive sleep apnea. **Endocrine. 2018 May;60(2):317-322. doi: 10.1007/s12020-018-1538-z. Epub 2018 Jan 31.** 1-6.
240. Colao A, Ferone D, Marzullo P & Lombardi G. Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 2004 **25** 102-152.
241. Hochban W, Ehlenz K, Conradt R & Brandenburg U. Obstructive sleep apnoea in acromegaly: the role of craniofacial changes. *European Respiratory Journal* 1999 **14** 196-202.

242. Kamenicky P, Viengchareun S, Blanchard A, Meduri G, Zizzari P, Imbert-Teboul M, Doucet A, Chanson P & Lombes M. Epithelial sodium channel is a key mediator of growth hormone-induced sodium retention in acromegaly. *Endocrinology* 2008 **149** 3294-3305.
243. Kamenicky P, Blanchard A, Frank M, Salenave S, Letierce A, Azizi M, Lombès M & Chanson P. Body Fluid Expansion in Acromegaly Is Related to Enhanced Epithelial Sodium Channel (ENaC) Activity. *The Journal of Clinical Endocrinology & Metabolism* 2011 **96** 2127-2135.
244. Quatresooz P, Hermanns-Le T, Ciccarelli A, Beckers A & Pierard GE. Tensegrity and type 1 dermal dendrocytes in acromegaly. *Eur J Clin Invest* 2005 **35** 133-139.
245. Chanson P & Salenave S. Acromegaly. *Orphanet Journal of Rare Diseases* 2008 **3** 17.
246. Herrmann B, Wessendorf T, Ajaj W, Kahlke S, Teschler H & Mann K. Effects of octreotide on sleep apnoea and tongue volume (magnetic resonance imaging) in patients with acromegaly. *European Journal of Endocrinology* 2004 **151** 309-315.
247. Dostalova S, Sonka K, Smahel Z, Weiss V, Marek J & Horinek D. Craniofacial abnormalities and their relevance for sleep apnoea syndrome aetiopathogenesis in acromegaly. *European Journal of Endocrinology* 2001 **144** 491-497.
248. van Haute FR, Taboada GF, Corrêa LL, Lima GA, Fontes R, Riello AP, Dominici M & Gadelha MR. Prevalence of sleep apnea and metabolic abnormalities in patients with acromegaly and analysis of cephalometric parameters by magnetic resonance imaging. *European Journal of Endocrinology* 2008 **158** 459-465.
249. Ip M, Tan K, Peh W & Lam K. Effect of Sandostatin® LAR® on sleep apnoea in acromegaly: correlation with computerized tomographic cephalometry and hormonal activity. *Clinical endocrinology* 2001 **55** 477-483.
250. Isono S, Saeki N, Tanaka A & Nishino T. Collapsibility of passive pharynx in patients with acromegaly. *Am J Respir Crit Care Med* 1999 **160** 64-68.
251. Attal P, Claes V, Bobin S, Chanson P, Kamenicky P, Zizzari P & Lecarpentier Y. Growth hormone excess and sternohyoid muscle mechanics in rats. *European Respiratory Journal* 2009 **34** 967-974.
252. Wolinski K, Stangierski A, Gurgul E, Brominska B, Czarnywojtek A, Lodyga M & Ruchala M. Thyroid lesions in patients with acromegaly - case-control study and update to the meta-analysis. *Endokrynol Pol* 2017 **68** 2-6.
253. Gasperi M, Martino E, Manetti L, Arosio M, Porretti S, Faglia G, Mariotti S, Colao A, Lombardi G & Baldelli R. Prevalence of thyroid diseases in patients with acromegaly: results of an Italian multi-center study. *Journal of endocrinological investigation* 2002 **25** 240-245.
254. Amado A, Araujo F & Carvalho D. Cardiovascular Risk Factors in Acromegaly: What's the Impact of Disease Control? *Exp Clin Endocrinol Diabetes* 2018.
255. Sze L, Schmid C, Bloch KE, Bernays R & Brändle M. Effect of transsphenoidal surgery on sleep apnoea in acromegaly. *European Journal of Endocrinology* 2007 **156** 321-329.
256. Zhang Z, Li Q, He W, Qiu H, Ye H, Wang Y, Shen M, He M, Yu Y & Shou X. The comprehensive impact on human body induced by resolution of growth hormone excess. *European Journal of Endocrinology* 2018 EJE-17-0872.
257. Tolis G, Angelopoulos NG, Katounda E, Rombopoulos G, Kaltzidou V, Kaltsas D, Protonotariou A & Lytras A. Medical treatment of acromegaly: comorbidities and their reversibility by somatostatin analogs. *Neuroendocrinology* 2006 **83** 249-257.
258. Grunstein RR, Ho KK & Sullivan CE. Effect of octreotide, a somatostatin analog, on sleep apnea in patients with acromegaly. *Ann Intern Med* 1994 **121** 478-483.
259. Chanson P, Timsit J, Benoit O, Augendre B, Moulonguet M, Guillausseau P-J, Warnet A & Lubetzki J. Rapid improvement in sleep apnoea of acromegaly after short-term treatment with somatostatin analogue SMS 201-995. *The Lancet* 1986 **327** 1270-1271.
260. Leibowitz G, Shapiro M, Salameh M & Glaser B. Improvement of sleep apnoea due to acromegaly during short-term treatment with octreotide. *Journal of internal medicine* 1994 **236** 231-235.

261. Berg C, Wessendorf T, Mortsch F, Forsting M, Teschler H, Weischer T, Mann K, Saller B & Herrmann B. Influence of disease control with pegvisomant on sleep apnoea and tongue volume in patients with active acromegaly. *European Journal of Endocrinology* 2009 **161** 829-835.
262. Kuhn E, Maione L, Bouchachi A, Rozière M, Salenave S, Brailly-Tabard S, Young J, Kamenicky P, Assayag P & Chanson P. Long-term effects of pegvisomant on comorbidities in patients with acromegaly: a retrospective single-center study. *European Journal of Endocrinology* 2015 **173** 693-702.
263. Chemla D, Attal P, Maione L, Veyer A-S, Mroue G, Baud D, Salenave S, Kamenicky P, Bobin S & Chanson P. Impact of successful treatment of acromegaly on overnight heart rate variability and sleep apnea. *The Journal of Clinical Endocrinology & Metabolism* 2014 **99** 2925-2931.
264. Melmed S, Casanueva F, Klibanski A, Bronstein M, Chanson P, Lamberts S, Strasburger C, Wass J & Giustina A. A consensus on the diagnosis and treatment of acromegaly complications. *Pituitary* 2013 **16** 294-302.
265. Peker Y, Svensson J, Hedner J, Grote L & Johannsson G. Sleep apnoea and quality of life in growth hormone (GH)-deficient adults before and after 6 months of GH replacement therapy. *Clinical endocrinology* 2006 **65** 98-105.
266. Ottosson M, Lönnroth P, Björntorp P & Edén S. Effects of Cortisol and Growth Hormone on Lipolysis in Human Adipose Tissue1. *The Journal of Clinical Endocrinology & Metabolism* 2000 **85** 799-803.
267. Bergan-Roller HE & Sheridan MA. The growth hormone signaling system: Insights into coordinating the anabolic and catabolic actions of growth hormone. *Gen Comp Endocrinol* 2018 **258** 119-133.
268. Nolte W, Rädisch C, Rodenbeck A, Wiltfang J & Hüfner M. Polysomnographic findings in five adult patients with pituitary insufficiency before and after cessation of human growth hormone replacement therapy. *Clinical endocrinology* 2002 **56** 805-810.
269. Hartman ML, Xu R, Crowe BJ, Robison LL, Erfurth EM, Kleinberg DL, Zimmermann AG, Woodmansee WW, Cutler Jr GB & Chipman JJ. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *The Journal of Clinical Endocrinology & Metabolism* 2013 **98** 980-988.
270. Karimi M, Koranyi J, Franco C, Peker Y, Eder DN, Angelhed J-E, Lönn L, Grote L, Bengtsson B-Å & Svensson J. Increased neck soft tissue mass and worsening of obstructive sleep apnea after growth hormone treatment in men with abdominal obesity. *Journal of clinical sleep medicine: JCSM: official publication of the American Academy of Sleep Medicine* 2010 **6** 256.
271. Sedky K, Bennett DS & Pumariega A. Prader Willi syndrome and obstructive sleep apnea: co-occurrence in the pediatric population. *J Clin Sleep Med* 2014 **10** 403-409.
272. Salvatoni A, Veronelli E, Nosetti L, Berini J, de Simone S, Iughetti L, Bosio L, Chiumello G, Grugni G, Delu G, Castelnuovo P, Trifiro G & Nespoli L. Short-term effects of growth hormone treatment on the upper airways of non severely obese children with Prader-Willi syndrome. *J Endocrinol Invest* 2009 **32** 601-605.
273. Miller J, Silverstein J, Shuster J, Driscoll DJ & Wagner M. Short-term effects of growth hormone on sleep abnormalities in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2006 **91** 413-417.
274. Berini J, Spica Russotto V, Castelnuovo P, Di Candia S, Gargantini L, Grugni G, Iughetti L, Nespoli L, Nosetti L, Padoan G, Pilotta A, Trifiro G, Chiumello G & Salvatoni A. Growth hormone therapy and respiratory disorders: long-term follow-up in PWS children. *J Clin Endocrinol Metab* 2013 **98** E1516-1523.
275. Al-Saleh S, Al-Naimi A, Hamilton J, Zweerink A, Iaboni A & Narang I. Longitudinal evaluation of sleep-disordered breathing in children with Prader-Willi Syndrome during 2 years of growth hormone therapy. *J Pediatr* 2013 **162** 263-268.e261.

276. Deal CL, Tony M, Hoybye C, Allen DB, Tauber M & Christiansen JS. GrowthHormone Research Society workshop summary: consensus guidelines for recombinant human growth hormone therapy in Prader-Willi syndrome. *J Clin Endocrinol Metab* 2013 **98** E1072-1087.
277. Stafler P & Wallis C. Prader-Willi syndrome: who can have growth hormone? *Arch Dis Child* 2008 **93** 341-345.
278. Nixon GM, Rodda CP & Davey MJ. Longitudinal association between growth hormone therapy and obstructive sleep apnea in a child with Prader-Willi syndrome. *J Clin Endocrinol Metab* 2011 **96** 29-33.
279. Riedl S, Blumel P, Zwiauer K & Frisch H. Death in two female Prader-Willi syndrome patients during the early phase of growth hormone treatment. *Acta Paediatr* 2005 **94** 974-977.
280. Grugni G, Livieri C, Corrias A, Sartorio A & Crino A. Death during GH therapy in children with Prader-Willi syndrome: description of two new cases. *J Endocrinol Invest* 2005 **28** 554-557.
281. Sorensen JR, Winther KH, Bonnema SJ, Godballe C & Hegedus L. Respiratory Manifestations of Hypothyroidism: A Systematic Review. *Thyroid* 2016 **26** 1519-1527.
282. Jha A, Sharma SK, Tandon N, Lakshmy R, Kadhiravan T, Handa KK, Gupta R, Pandey RM & Chaturvedi PK. Thyroxine replacement therapy reverses sleep-disordered breathing in patients with primary hypothyroidism. *Sleep Med* 2006 **7** 55-61.
283. Resta O, Carratu P, Carpagnano G, Maniscalco M, Di Gioia G, Lacedonia D, Giorgino R & De Pergola G. Influence of subclinical hypothyroidism and T~ 4 treatment on the prevalence and severity of obstructive sleep apnoea syndrome (OSAS). *Journal of endocrinological investigation* 2005 **28** 893.
284. Al-Jawder SE & BaHammam AS. Hypothyroidism and Obstructive Sleep Apnea. In *Hypothyroidism-Influences and Treatments*: InTech, 2012.
285. Mete T, Yalcin Y, Berker D, Ciftci B, Firat SG, Topaloglu O, Yavuz HC & Guler S. Relationship between obstructive sleep apnea syndrome and thyroid diseases. *Endocrine* 2013 **44** 723-728.
286. Bielicki P, Przybyłowski T, Kumor M, Barnaś M, Wiercioch M & Chazan R. Thyroid hormone levels and TSH activity in patients with obstructive sleep apnea syndrome. In *Advances in Clinical Science*, pp 67-71: Springer, 2015.
287. Resta O, Pannacciulli N, Di Gioia G, Stefano A, Barbaro MF & De Pergola G. High prevalence of previously unknown subclinical hypothyroidism in obese patients referred to a sleep clinic for sleep disordered breathing. *Nutrition, Metabolism and Cardiovascular Diseases* 2004 **14** 248-253.
288. Bahammam SA, Sharif MM, Jammah AA & BaHammam AS. Prevalence of thyroid disease in patients with obstructive sleep apnea. *Respir Med* 2011 **105** 1755-1760.
289. Ozcan KM, Selcuk A, Ozcan I, Ozdas T, Ozdogan F, Acar M & Dere H. Incidence of hypothyroidism and its correlation with polysomnography findings in obstructive sleep apnea. *European Archives of Oto-Rhino-Laryngology* 2014 **271** 2937-2941.
290. Takeuchi S, Kitamura T, Ohbuchi T, Koizumi H, Takahashi R, Hohchi N & Suzuki H. Relationship between sleep apnea and thyroid function. *Sleep and Breathing* 2015 **19** 85-89.
291. Bozkurt NC, Karbek B, Cakal E, Firat H, Ozbek M & Delibasi T. The association between severity of obstructive sleep apnea and prevalence of Hashimoto's thyroiditis. *Endocrine journal* 2012 **59** 981-988.
292. Hegedüs L, Hansen JM, Feldt-Rasmussen U, Hansen BM & Høier-Madsen M. Influence of thyroxine treatment on thyroid size and anti-thyroid peroxidase antibodies in Hashimoto's thyroiditis. *Clinical endocrinology* 1991 **35** 235-238.
293. Gutierrez T, Leong A, Pang L, Chevretton E, Jeannon J & Simo R. Multinodular thyroid goitre causing obstructive sleep apnoea syndrome. *The Journal of laryngology and otology* 2012 **126** 190.
294. Menon SK, Jagtap VS, Sarathi V, Lila AR, Bandgar TR, Menon PS & Shah NS. Prevalence of upper airway obstruction in patients with apparently asymptomatic euthyroid multi nodular goitre. *Indian J Endocrinol Metab* 2011 **15** S127.

295. Schlenker EH & Schultz HD. Hypothyroidism attenuates SCH 23390-mediated depression of breathing and decreases D1 receptor expression in carotid bodies, PVN and striatum of hamsters. *Brain research* 2011 **1401** 40-51.
296. Petrof BJ, Kelly AM, Rubinstein NA & Pack AI. Effect of hypothyroidism on myosin heavy chain expression in rat pharyngeal dilator muscles. *J Appl Physiol (1985)* 1992 **73** 179-187.
297. Geiger PC, Cody MJ, Han YS, Hunter LW, Zhan W-Z & Sieck GC. Effects of hypothyroidism on maximum specific force in rat diaphragm muscle fibers. *Journal of Applied Physiology* 2002 **92** 1506-1514.
298. Laurberg P, Knudsen N, Andersen S, Carlé A, Pedersen IB & Karmisholt J. Thyroid function and obesity. *European thyroid journal* 2012 **1** 159-167.
299. Sánchez A, Carretto H, Ulla MR & Capozza R. Body composition of patients with primary hypothyroidism evaluated by dual-energy X-ray absorptiometry and its changes after treatment with levo-thyroxine. *The Endocrinologist* 2004 **14** 321-327.
300. Karmisholt J, Andersen S & Laurberg P. Weight loss after therapy of hypothyroidism is mainly caused by excretion of excess body water associated with myxoedema. *The Journal of Clinical Endocrinology & Metabolism* 2011 **96** E99-E103.
301. Petrone A, Mormile F, Bruni G, Quartieri M, Bonsignore MR & Marrone O. Abnormal thyroid hormones and non-thyroidal illness syndrome in obstructive sleep apnea, and effects of CPAP treatment. *Sleep Med* 2016 **23** 21-25.
302. Peeters RP, Wouters PJ, Kaptein E, Van Toor H, Visser TJ & Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *The Journal of Clinical Endocrinology & Metabolism* 2003 **88** 3202-3211.
303. DeGroot LJ. The non-thyroidal illness syndrome. *Elsevier, USA* 2015.
304. Xu G, Yan W & Li J. An update for the controversies and hypotheses of regulating nonthyroidal illness syndrome in chronic kidney diseases. *Clinical and experimental nephrology* 2014 **18** 837-843.
305. Punjabi NM. The epidemiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008 **5** 136-143.
306. Lanfranco F, Motta G, Minetto MA, Baldi M, Balbo M, Ghigo E, Arvat E & Maccario M. Neuroendocrine alterations in obese patients with sleep apnea syndrome. *International Journal of Endocrinology* 2010 **2010**.
307. Barrett-Connor E, Dam T-T, Stone K, Harrison SL, Redline S, Orwoll E & Group OFiMS. The association of testosterone levels with overall sleep quality, sleep architecture, and sleep-disordered breathing. *The Journal of Clinical Endocrinology & Metabolism* 2008 **93** 2602-2609.
308. Luboshitzky R, Aviv A, Hefetz A, Herer P, Shen-Orr Z, Lavie L & Lavie P. Decreased Pituitary-Gonadal Secretion in Men with Obstructive Sleep Apnea. *The Journal of Clinical Endocrinology & Metabolism* 2002 **87** 3394-3398.
309. Yee B, Liu P, Phillips C & Grunstein R. Neuroendocrine changes in sleep apnea. *Curr Opin Pulm Med* 2004 **10** 475-481.
310. Gambineri A, Pelusi Ca & Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. *Journal of endocrinological investigation* 2003 **26** 493-498.
311. Luboshitzky R, Lavie L, Shen-Orr Z & Herer P. Altered Luteinizing Hormone and Testosterone Secretion in Middle-Aged Obese Men with Obstructive Sleep Apnea. *Obesity* 2005 **13** 780-786.
312. Cole AP, Hanske J, Jiang W, Kwon NK, Lipsitz SR, Kathrins M, Learn PA, Sun M, Haider AH & Basaria S. Impact of testosterone replacement therapy on thromboembolism, heart disease and obstructive sleep apnoea in men. *BJU international* 2018.

313. Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR & Handelsman DJ. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *The Journal of Clinical Endocrinology & Metabolism* 2003 **88** 3605-3613.
314. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J & Kapoor SC. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *The Journal of Clinical Endocrinology & Metabolism* 1999 **84** 1966-1972.
315. Schneider BK, Pickett CK, Zwillich CW, Weil JV, McDermott MT, Santen RJ, Varano LA & White DP. Influence of testosterone on breathing during sleep. *Journal of Applied Physiology* 1986 **61** 618-623.
316. Matsumoto A, Sandblom R, Schoene R, LEE KA, GIBLIN EC, Pierson D & Bremner W. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnoea, respiratory drives, and sleep. *Clinical endocrinology* 1985 **22** 713-721.
317. Sandblom RE, Matsumoto AM, Schoene RB, Lee KA, Giblin EC, Bremner WJ & Pierson DJ. Obstructive sleep apnea syndrome induced by testosterone administration. *New England Journal of Medicine* 1983 **308** 508-510.
318. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, Snyder PJ, Swerdloff RS, Wu FC & Yialamas MA. Testosterone Therapy in Men With Hypogonadism: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2018.
319. Hoyos CM, Killick R, Yee BJ, Grunstein RR & Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. *Clinical endocrinology* 2012 **77** 599-607.
320. Killick R, Wang D, Hoyos CM, Yee BJ, Grunstein RR & Liu PY. The effects of testosterone on ventilatory responses in men with obstructive sleep apnea: a randomised, placebo-controlled trial. *J Sleep Res* 2013 **22** 331-336.
321. Yuki A, Otsuka R, Kozakai R, Kitamura I, Okura T, Ando F & Shimokata H. Relationship between low free testosterone levels and loss of muscle mass. *Sci Rep* 2013 **3** 1818.
322. Kelly DM & Jones TH. Testosterone and obesity. *Obes Rev* 2015 **16** 581-606.
323. Andersen ML & Tufik S. The effects of testosterone on sleep and sleep-disordered breathing in men: its bidirectional interaction with erectile function. *Sleep Med Rev* 2008 **12** 365-379.
324. Burschtin O & Wang J. Testosterone Deficiency and Sleep Apnea. *Sleep Med Clin* 2016 **11** 525-529.
325. Stewart DA, Grunstein RR, Berthon-Jones M, Handelsman DJ & Sullivan CE. Androgen blockade does not affect sleep-disordered breathing or chemosensitivity in men with obstructive sleep apnea. *Am Rev Respir Dis* 1992 **146** 1389-1393.
326. Luboshitzky R, Zabari Z, Shen-Orr Z, Herer P & Lavie P. Disruption of the nocturnal testosterone rhythm by sleep fragmentation in normal men. *The Journal of Clinical Endocrinology & Metabolism* 2001 **86** 1134-1139.
327. Zhang X-B, Jiang X-T, Du Y-P, Yuan Y-T & Chen B. Efficacy of continuous positive airway pressure on testosterone in men with obstructive sleep apnea: a meta-analysis. *PLoS ONE* 2014 **9** e115033.
328. Bratel T, Wennlund A & Carlström K. Pituitary reactivity, androgens and catecholamines in obstructive sleep apnoea. Effects of continuous positive airway pressure treatment (CPAP). *Respir Med* 1999 **93** 1-7.
329. Luboshitzky R, Lavie L, Shen-Orr Z & Lavie P. Pituitary-gonadal function in men with obstructive sleep apnea. *Neuro Endocrinol Lett* 2003 **24** 463-467.
330. Celec P, Mucska I, Ostatnikova D & Hodosy J. Testosterone and estradiol are not affected in male and female patients with obstructive sleep apnea treated with continuous positive airway pressure. *Journal of endocrinological investigation* 2014 **37** 9-12.
331. Knapp A, Myhill PC, Davis WA, Peters KE, Hillman D, Hamilton EJ, Lim EM & Davis TM. Effect of continuous positive airway pressure therapy on sexual function and serum testosterone in

males with type 2 diabetes and obstructive sleep apnoea. *Clinical endocrinology* 2014 **81** 254-258.
332. Hoekema A, Stel AL, Stegenga B, Van Der Hoeven JH, Wijkstra PJ, Van Driel MF & De Bont LG. Sexual function and obstructive sleep apnea–hypopnea: A randomized clinical trial evaluating the effects of oral-appliance and continuous positive airway pressure therapy. *The journal of sexual medicine* 2007 **4** 1153-1162.
333. Zhang X-B, Lin Q-C, Zeng H-Q, Jiang X-T, Chen B & Chen X. Erectile dysfunction and sexual hormone levels in men with obstructive sleep apnea: efficacy of continuous positive airway pressure. *Archives of sexual behavior* 2016 **45** 235-240.
334. Li Z, Tang T, Wu W, Gu L, Du J, Zhao T, Zhou X, Wu H & Qin G. Efficacy of nasal continuous positive airway pressure on patients with OSA with erectile dysfunction and low sex hormone levels. *Respir Med* 2016 **119** 130-134.
335. Santamaria J, Prior J & Fleetham J. Reversible reproductive dysfunction in men with obstructive sleep apnoea. *Clinical endocrinology* 1988 **28** 461-470.
336. Pastore A, Palleschi G, Ripoli A, Silvestri L, Maggioni C, Pagliuca G, Nobili Benedetti F, Gallo A, Zucchi A & Maurizi A. Severe obstructive sleep apnoea syndrome and erectile dysfunction: a prospective randomised study to compare sildenafil vs. nasal continuous positive airway pressure. *Int J Clin Pract* 2014 **68** 995-1000.
337. Perimenis P, Karkoulias K, Markou S, Gyftopoulos K, Athanasopoulos A, Barbalias G, Kiriazopoulou V & Spiropoulos K. Erectile dysfunction in men with obstructive sleep apnea syndrome: a randomized study of the efficacy of sildenafil and continuous positive airway pressure. *International journal of impotence research* 2004 **16** 256.
338. Behan M & Wenninger JM. Sex steroidal hormones and respiratory control. *Respir Physiol Neurobiol* 2008 **164** 213-221.
339. Potvin C, Rossignol O, Uppari N, Dallongeville A, Bairam A & Joseph V. Reduced hypoxic ventilatory response in newborn mice knocked-out for the progesterone receptor. *Exp Physiol* 2014 **99** 1523-1537.
340. Driver HS, Mclean H, Kumar DV, Farr N, Day AG & Fitzpatrick MF. The influence of the menstrual cycle on upper airway resistance and breathing during sleep. *Sleep* 2005 **28** 449-456.
341. Netzer NC, Eliasson AH & Strohl KP. Women with sleep apnea have lower levels of sex hormones. *Sleep and Breathing* 2003 **7** 25-29.
342. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, O'Connor GT, Rapoport DM & Robbins JA. Hormone replacement therapy and sleep-disordered breathing. *Am J Respir Crit Care Med* 2003 **167** 1186-1192.
343. Subramanian S, Bopparaju S, Desai A, Wiggins T, Rambaud C & Surani S. Sexual dysfunction in women with obstructive sleep apnea. *Sleep and Breathing* 2010 **14** 59-62.
344. Petersen M, Kristensen E, Berg S, Giraldi A & Midgren B. Sexual function in female patients with obstructive sleep apnea. *The journal of sexual medicine* 2011 **8** 2560-2568.
345. Stavaras C, Pastaka C, Papala M, Gravas S, Tzortzis V, Melekos M, Seitanidis G & Gourgoulianis K. Sexual function in pre-and post-menopausal women with obstructive sleep apnea syndrome. *International journal of impotence research* 2012 **24** 228.
346. Steinke E, Palm Johansen P, Fridlund B & Brostrom A. Determinants of sexual dysfunction and interventions for patients with obstructive sleep apnoea: a systematic review. *Int J Clin Pract* 2016 **70** 5-19.
347. Kahal H, Kyrou I, Uthman O, Brown A, Johnson S, Wall P, Metcalfe A, Tahrani A & Randeva H. The Prevalence of Obstructive Sleep Apnoea in women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis. *Endocrine Abstracts (2017) 50 P339 | DOI: 10.1530/endoabs.50.P339* 2017.

348. Kang K-T, Chou C-H, Weng W-C, Lee P-L & Hsu W-C. Associations between adenotonsillar hypertrophy, age, and obesity in children with obstructive sleep apnea. *PLoS ONE* 2013 **8** e78666.
349. Kahal H, Kyrou I, Uthman O, Brown A, Johnson S, Wall P, Metcalfe A, Tahrani AA & Randeva HS. The Association between Obstructive Sleep Apnoea and Metabolic Abnormalities in Women with Polycystic Ovary Syndrome: a Systematic Review and Meta-analysis. *Sleep* 2018 zsy085-zsy085.
350. Kahal H, Kyrou I, Tahrani AA & Randeva HS. Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; a comprehensive review of clinical interactions and underlying pathophysiology. *Clinical endocrinology* 2017.
351. Uzkeser H, Yildirim K, Aktan B, Karatay S, Kaynar H, Araz O & Kilic K. Bone mineral density in patients with obstructive sleep apnea syndrome. *Sleep and Breathing* 2013 **17** 339-342.
352. Terzi R & Yılmaz Z. Bone mineral density and changes in bone metabolism in patients with obstructive sleep apnea syndrome. *Journal of bone and mineral metabolism* 2016 **34** 475-481.
353. Mariani S, Fiore D, Varone L, Basciani S, Persichetti A, Watanabe M, Saponara M, Spera G, Moretti C & Gnessi L. Obstructive sleep apnea and bone mineral density in obese patients. *Diabetes, metabolic syndrome and obesity: targets and therapy* 2012 **5** 395.
354. Sforza E, Thomas T, Barthelemy JC, Collet P & Roche F. Obstructive sleep apnea is associated with preserved bone mineral density in healthy elderly subjects. *Sleep* 2013 **36** 1509-1515.
355. Chen Y-L, Weng S-F, Shen Y-C, Chou C-W, Yang C-Y, Wang J-J & Tien K-J. Obstructive sleep apnea and risk of osteoporosis: a population-based cohort study in Taiwan. *The Journal of Clinical Endocrinology & Metabolism* 2014 **99** 2441-2447.
356. Yen C-M, Kuo C-L, Lin M-C, Lee C-F, Lin K-Y, Lin C-L, Chang S-N, Sung F-C & Kao C-H. Sleep disorders increase the risk of osteoporosis: a nationwide population-based cohort study. *Sleep Med* 2014 **15** 1339-1344.
357. Cauley JA, Blackwell TL, Redline S, Ensrud KE, Ancoli-Israel S, Fink HA, Orwoll ES & Stone KL. Hypoxia during sleep and the risk of falls and fractures in older men: the Osteoporotic Fractures in Men Sleep Study. *Journal of the American Geriatrics Society* 2014 **62** 1853-1859.
358. Stone KL, Ewing SK, Lui LY, Ensrud KE, Ancoli-Israel S, Bauer DC, Cauley JA, Hillier TA & Cummings SR. Self-reported sleep and nap habits and risk of falls and fractures in older women: the study of osteoporotic fractures. *Journal of the American Geriatrics Society* 2006 **54** 1177-1183.
359. Choi SB, Lyu IS, Lee W & Kim DW. Increased fragility fracture risk in Korean women who snore: a 10-year population-based prospective cohort study. *BMC Musculoskelet Disord* 2017 **18** 236.
360. Tomiyama H, Okazaki R, Inoue D, Ochiai H, Shiina K, Takata Y, Hashimoto H & Yamashina A. Link between obstructive sleep apnea and increased bone resorption in men. *Osteoporosis International* 2008 **19** 1185-1192.
361. Maes C, Carmeliet G & Schipani E. Hypoxia-driven pathways in bone development, regeneration and disease. *Nature Reviews Rheumatology* 2012 **8** 358.
362. Fan L, Li J, Yu Z, Dang X & Wang K. The hypoxia-inducible factor pathway, prolyl hydroxylase domain protein inhibitors, and their roles in bone repair and regeneration. *BioMed Research International* 2014 **2014**.
363. Knowles HJ & Athanasou NA. Acute hypoxia and osteoclast activity: a balance between enhanced resorption and increased apoptosis. *The Journal of pathology* 2009 **218** 256-264.
364. Frey JL, Stonko DP, Faugere M-C & Riddle RC. Hypoxia-inducible factor-1α restricts the anabolic actions of parathyroid hormone. *Bone research* 2014 **2** 14005.
365. Zelzer E & Olsen BR. 6 Multiple Roles of Vascular Endothelial Growth Factor (VEGF) in Skeletal Development, Growth, and Repair. *Current topics in developmental biology* 2005 **65** 170-188.

366. Barbour KE, Boudreau R, Danielson ME, Youk AO, Wactawski-Wende J, Greep NC, LaCroix AZ, Jackson RD, Wallace RB & Bauer DC. Inflammatory markers and the risk of hip fracture: the Women's Health Initiative. *Journal of Bone and Mineral Research* 2012 **27** 1167-1176.
367. Cauley JA, Danielson ME, Boudreau RM, Forrest KY, Zmuda JM, Pahor M, Tylavsky FA, Cummings SR, Harris TB & Newman AB. Inflammatory markers and incident fracture risk in older men and women: the Health Aging and Body Composition Study. *Journal of Bone and Mineral Research* 2007 **22** 1088-1095.
368. Sheweita S & Khoshhal K. Calcium metabolism and oxidative stress in bone fractures: role of antioxidants. *Current drug metabolism* 2007 **8** 519-525.
369. Pan W & Kastin AJ. Leptin: a biomarker for sleep disorders? *Sleep Med Rev* 2014 **18** 283-290.
370. Swanson CM, Shea SA, Stone KL, Cauley JA, Rosen CJ, Redline S, Karsenty G & Orwoll ES. Obstructive sleep apnea and metabolic bone disease: insights into the relationship between bone and sleep. *Journal of Bone and Mineral Research* 2015 **30** 199-211.
371. Barnas M, Maskey-Warzechowska M, Bielicki P, Kumor M & Chazan R. Diurnal and nocturnal serum melatonin concentrations after treatment with continuous positive airway pressure in patients with obstructive sleep apnea. *Pol Arch Intern Med* 2017 **127** 589-596.
372. Amstrup AK, Sikjaer T, Heickendorff L, Mosekilde L & Rejnmark L. Melatonin improves bone mineral density at the femoral neck in postmenopausal women with osteopenia: a randomized controlled trial. *Journal of pineal research* 2015 **59** 221-229.
373. Liguori C, Romigi A, Izzi F, Mercuri N, Cordella A, Tarquini E, Giambrone M, Marciani M & Placidi F. Erratum: Continuous positive airway pressure treatment increases serum Vitamin D levels in male patients with obstructive sleep apnea (Journal of Clinical Sleep Medicine (2015) 11: 6 (603-607)). *Journal of Clinical Sleep Medicine* 2015 **11** 1349.
374. Dede AD, Tournis S, Dontas I & Trovas G. Type 2 diabetes mellitus and fracture risk. *Metabolism* 2014 **63** 1480-1490.
375. Tanaka H, Yamashita T, Yoneda M, Takagi S & Miura T. Characteristics of bone strength and metabolism in type 2 diabetic model Tsumura, Suzuki, Obese Diabetes mice. *Bone Rep* 2018 **9** 74-83.
376. Chen FP, Kuo SF, Lin YC, Fan CM & Chen JF. Status of bone strength and factors associated with vertebral fracture in postmenopausal women with type 2 diabetes. *Menopause* 2018 **Menopause. 2018 Aug 20. doi: 10.1097/GME.0000000000001185**.
377. Ferrari SL, Abrahamsen B, Napoli N, Akesson K, Chandran M, Eastell R, El-Hajj Fuleihan G, Josse R, Kendler DL, Kraenzlin M, Suzuki A, Pierroz DD, Schwartz AV & Leslie WD. Diagnosis and management of bone fragility in diabetes: an emerging challenge. *Osteoporos Int* 2018.

Figures-Legends & text:

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

Figure 2: OSA & 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. Red boxes are the mechanisms of OSA that might lead to weight gain; Dark

blue boxes are the mechanisms of possible weight loss in OSA. UA: Upper Airways; TNF-A: Tumour Necrosis Factor- Alpha; IL-6: 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[19-27]. 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]. ~~Obesity is also associated with leptin resistance, which could inhibit the respiratory drive as leptin is a respiratory stimulant[23, 29-31]. Furthermore, visceral adiposity can affect the neural respiratory control and the responsiveness of the chemoreceptors, through neurohormonal and inflammatory mechanisms (such as (TNF) a, and IL-6)[26, 30, 32], but OSA itself can further worsen inflammation and possibly oxidative stress, therefore, leading to a vicious cycle[23, 26, 33].~~

Figure 3: The potential bi-directional 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: Non-Alcoholic 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 β- cell dysfunction. In addition, OSA can ~~impact multiple hormones that can~~ lead to dysglycaemia ~~including: 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, 90-95]. 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[97-101]. Furthermore, patients with OSA (due to recurrent microarousals, the loss of SWS and the IH[59]) have increased sympathetic activity which can contribute to the increased IR[30, 102]. ~~Several factors contribute to the sympathetic overactivation in OSA including the recurrent microarousals, the loss of SWS and the IH[59]~~. The IH, via oxidative stress and its impact on HIF signaling, 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

Formatted: Not Highlight

Formatted: Not Strikethrough

increased risk of Non-alcoholic 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 ~~(based on liver enzymes and histology)~~[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 ~~(forced vital capacity FVC, Forced Expiratory Volume in the first second FEV1 and vital capacity VC)~~ and functions compared to healthy individuals which could affect UA stability[111-121]. ~~A meta-analysis of cross-sectional studies showed that diabetes is associated with a modest but significant impairment of pulmonary function (in restrictive pattern)~~[122] 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 ~~but this needs to be examined~~. 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 apneas 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].

Figure 4: A. Mechanisms relating obstructive sleep apnoea to cardiovascular disease (A) and microvascular complications Adapted from Jullian-Desayes et al. with permission **(B) in patients with Type 2 diabetes**. Adapted from Tahrani et al. with permission. CRP: C-reactive protein; IH: intermittent hypoxia; NO: nitric oxide; NOx: total nitrate and nitrite; OSA: obstructive sleep apnea; PKC: protein kinase C; AGE: advanced glycation end product; PARP: poly ADP ribose polymerase; AR: aldose reductase; GAPDH: glyceraldehyde 3-phosphate dehydrogenase.

Fig. 4.A. Obstructive sleep apnea and its cardiometabolic consequences.. Adapted from Kohler et al., 2010 and Lavie et al., 2009[140]. 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

Formatted: Not Highlight

Formatted: Not Strikethrough

Formatted: Not Strikethrough

Formatted: Not Highlight

Formatted: Not Highlight

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].

Fig. 4.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].

Figure 5: The potential bi-directional 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[169, 170,159]. 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 ~~by further better designed studies of larger sample size~~ as the current studies show a non-significant trend.

The ~~plausible mechanisms for the~~ increased risk of OSA in patients with hyperaldosteronism ~~are~~ is plausible due to ~~the~~ increased sodium and fluid retention resulting in UA oedema, increased UA resistance and collapse[159, 176-178]. This might have been worsened further by ~~increases in neck circumference and~~ oedema due to fluid displacement during recumbency overnight particularly in patients with RH[159, 178] ~~, which is supported by a study showing a reduction in neck circumference with improvements in AHI after treatment of PA with either MR antagonist or adrenalectomy[172]~~.

Formatted: Not Highlight

Formatted: Not Highlight

Formatted: Not Highlight

Figure 6: OSA & HPA axis dysregulation A. Possible underlying mechanisms linking OSA to HPA axis dysregulation **B.** Possible mechanisms linking hypercortisolism with OSA development CRH: Corticotropin Releasing Hormone, ACTH: Adrenocorticotropic hormone

Figure 7: OSA & GH/IGF axis. A. Possible underlying mechanisms for OSA leading to GH/IGF axis dysregulation. **B.** Possible mechanisms linking GH excess (red arrows) and GH deficiency (blue arrows) with OSA development.

The main causal mechanisms linking acromegaly to OSA are related to the anatomical changes that occur as a result of GH excess leading to narrower and more collapsible UAs. Patients with acromegaly have vertical growth of the mandible, which leads to pharyngeal obstruction due to the retroposition of the tongue base with caudal displacement of the hyoid[225]. In addition, soft tissue thickening/swelling, secondary to increased glycosaminoglycan deposition, collagen and tissue oedema, and macroglossia contribute to the compromise of UAs in patients with acromegaly[226-234]. This is supported by a study using MRI and nasopharyngoscopy that showed the tongue base and uvula to be the main site of UA obstruction in patients with OSA and acromegaly[216]. In addition, the uvula diameter correlated to the severity of the UA collapse and tongue measurements correlated to the AHI and IGF-1 levels[216, 230]. The weakness of UA muscles (sternohyoid muscle) also contributes to the increased risk of UA collapsibility in patients with acromegaly[235]. Other factors include hypothyroidism, large goiters (detailed later)[219, 236, 237], insulin resistance and dysglycaemia[219, 224, 238].

Figure 8: Mechanisms linking OSA and Hypothyroidism

Hypothyroidism can lead to increased UA collapsibility due to soft tissue swelling (in tongue, neck, and pharynx) caused by mucopolysaccharides infiltration (myxoedema in the more severe form)[256]. In support of this mechanism, LT4 treatment reduced soft tissue swelling and improved AHI, nocturnal hypoxaemia and sleep architecture in an uncontrolled study[254]. Goitre (regardless of thyroid status) can cause UA obstruction and collapse[256, 263]. It causes narrowing of the UA by direct mechanical obstruction, especially in supine position, and by increasing laryngeal oedema due to reduced venous return; both of which can be resolved following thyroidectomy or LT4 in some cases[256, 264-266]. Hypothyroidism (especially when severe) can also result in blunted ventilatory drive and impaired chemosensors' response to hypoxia/ hypercapnia in animal and human studies[256]. This is possibly due to decreased dopamine receptor (D1) expression in the brain stem and the CB in rodents with hypothyroidism[267], and can be reversed with LT4 treatment[256].

Impaired UA dilator muscle function in hypothyroidism, due to altered myosin heavy chain expression in rodent studies and neuropathy in humans, has also been reported[217, 268]. Furthermore, the diaphragm has been shown to be weaker in rodents and human studies in hypothyroidism, which

result in a reduction in lung volumes contributing to OSA development/worsening [253, 256, 269]. The diaphragm weakness can be improved by LT4 treatment [253]. Finally, obesity could be potentially another link between OH and OSA as studies have shown that patients with OH are about 5-7kg heavier compared to euthyroid matched-controlled [270]. However, this weight-increase in OH seems to be related to expanded water compartment rather than fat mass. In addition, LT4 treatment causes weight loss by reducing lean mass rather than fat mass (based on DXA) [271, 272].

Figure 9: Obstructive Sleep Apnoea and Polycystic Ovary Syndrome; clinical interactions and underlying pathophysiology. Adapted from Kahal et al. with permission.

Formatted: Not Highlight

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 dysglycamia 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].

Figure 10: OSA & Bone metabolism.

GH: Growth hormone, PTH: Parathormone, BMD: Bone mineral density, BRMs: Bone Resorption Markers

As with other endocrine consequences of OSA, hypoxaemia plays an important role as has been shown by Cauley et al and IH in human cell cultures and rodents can increase osteoclasts and inhibit osteoblasts' growth and differentiation via HIF transcription factor family (HIF-1a and HIF-2a) and VEGF [333-337]. In addition, IH can result in increased inflammation and oxidative stress that can lead to higher risk of osteoporosis and fractures [338-340]. Other mechanisms including hyperleptinaemia and sympathetic activation increase bone resorption and inhibit bone formation leading to bone mass loss [341, 342]. Changes in melatonin profile could also contribute to the impact of OSA on bones, as patients with OSA might have changed melatonin profile and lower melatonin serum levels compared to people without OSA due to frequent nocturnal awakening and light exposure [343]. Melatonin has

been shown to increase bone mass density in a RCT[344]. Furthermore, serum 25-hydroxyvitamin D was found to be lower (: 19.34 ± 9.54 ng/ml vs. 32.83 ± 16.93 ng/ml, $p < 0.0001$) and PTH levels higher (: 62.57 ± 29.97 pg/mL vs. 40.05 ± 31.12 pg/mL, $p < 0.0001$) in patients with OSA compared to healthy controls[345]. CPAP for 7 nights increased 25-hydroxyvitamin D concentrations (19.21 ± 9.45 vs. 21.03 ± 9.50, $F = 8.32$, $p < 0.01$) but had no effect on PTH[345]. The suppression of the gonadal axis and GH in OSA and the associated insulin resistance could also contribute to the impact of OSA on bone metabolism[342]. T2D in particular can have detrimental effects on bone mass and fracture risk[374-377] and as OSA increases the risk of T2D, then T2D is a potential mechanism between OSA and bone disease.

Formatted: Not Highlight

Field Code Changed

Formatted: Not Highlight

Formatted: Not Highlight

Figure 1

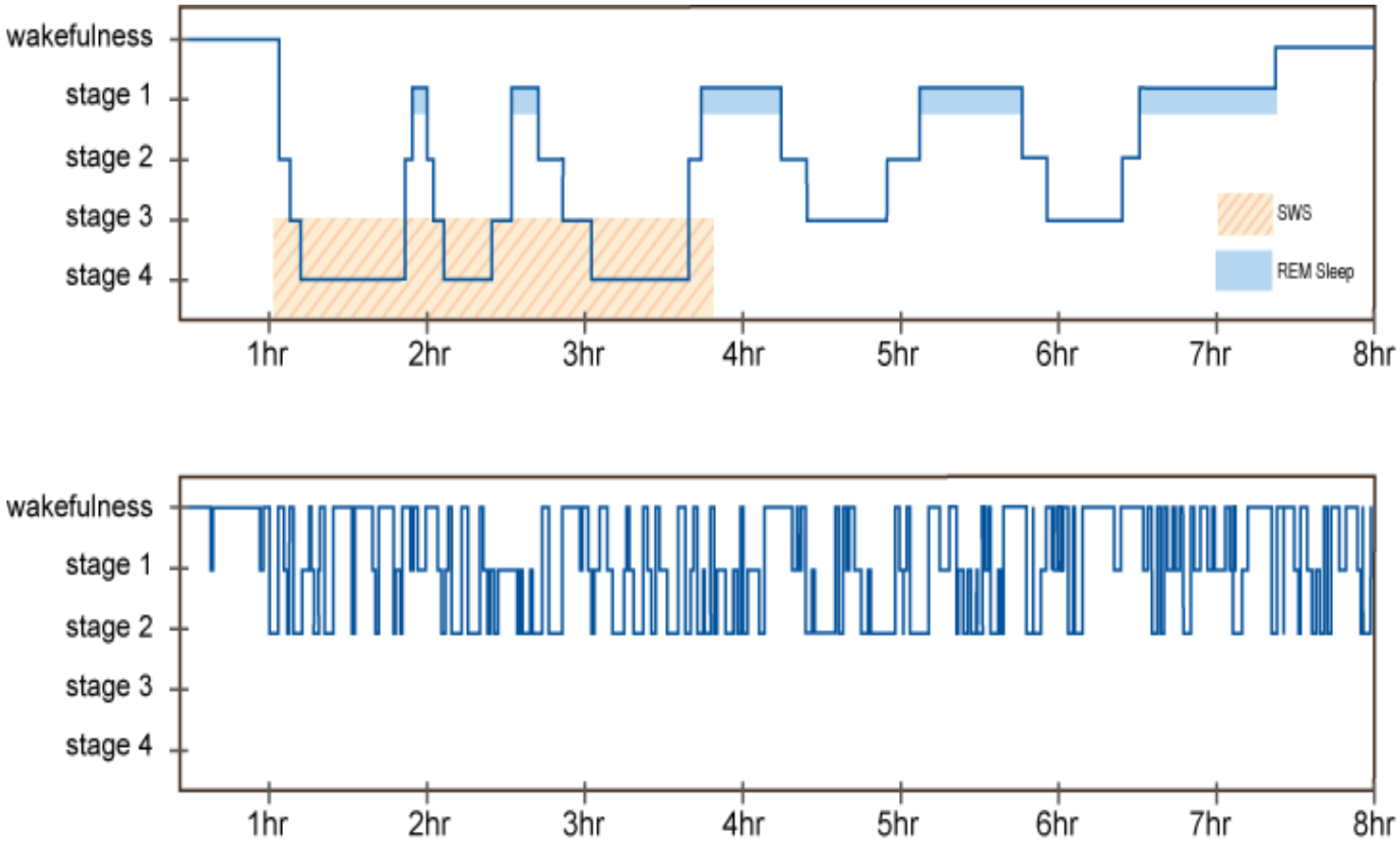

wakefulness
stage 1
stage 2
stage 3
stage 4
SWS
REM Sleep
1hr
2hr
3hr
4hr
5hr
6hr
7hr
8hr
wakefulness
stage 1
stage 2
stage 3
stage 4
1hr
2hr
3hr
4hr
5hr
6hr
7hr
8hr

Figure 2

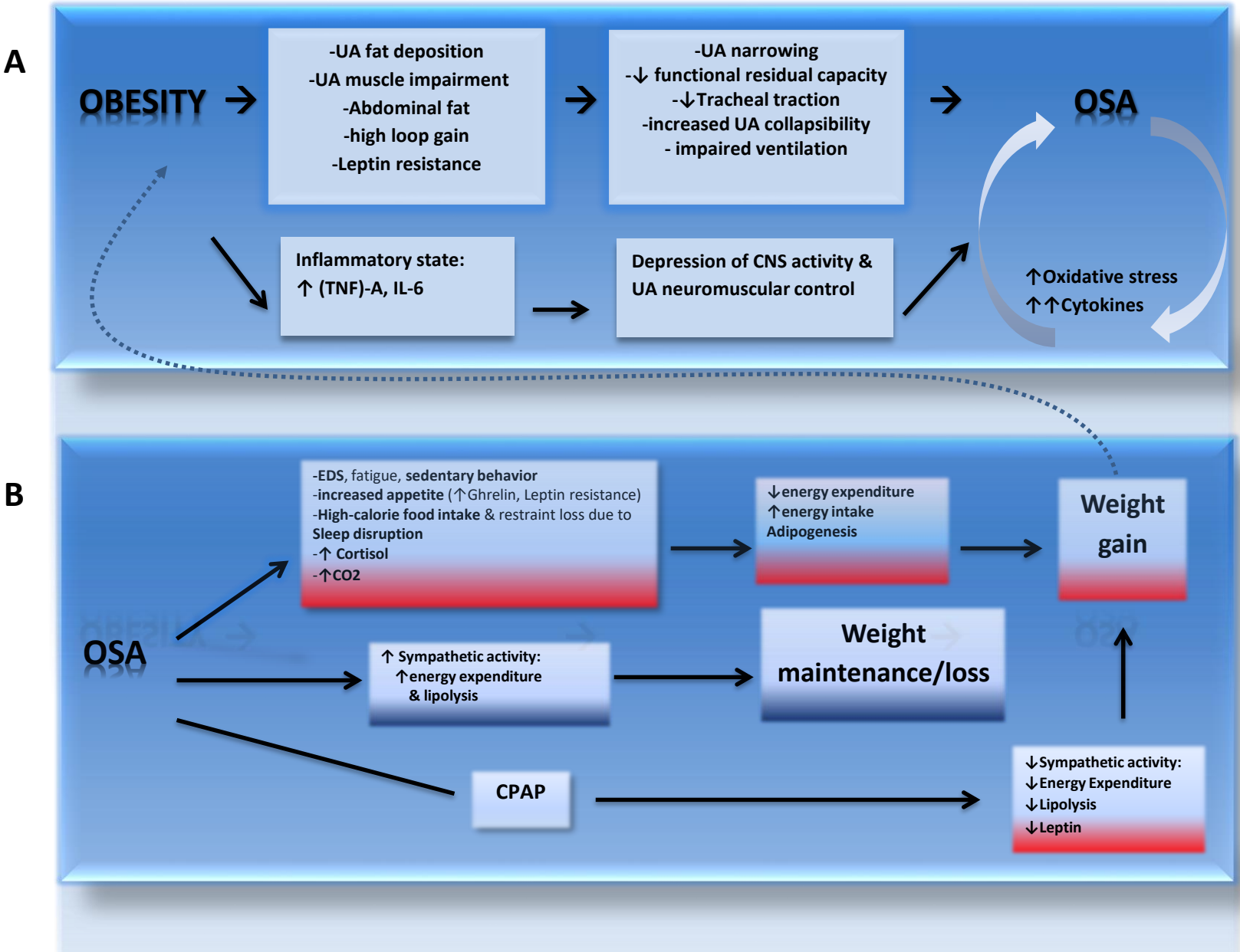

A
OBESITY
-UA fat deposition
-UA muscle impairment
-Abdominal fat
-high loop gain
-Leptin resistance
-UA narrowing
-↓ functional residual capacity
-↓Tracheal traction
-increased UA collapsibility
- impaired ventilation
OSA
Inflammatory state:
↑ (TNF)-A, IL-6
Depression of CNS activity &
UA neuromuscular control
↑Oxidative stress
↑↑Cytokines
B
OSA
-EDS, fatigue, sedentary behavior
-increased appetite (↑Ghrelin, Leptin resistance)
-High-calorie food intake & restraint loss due to Sleep disruption
-↑ Cortisol
-↑CO2
↓energy expenditure
↑energy intake
Adipogenesis
Weight gain
↑ Sympathetic activity:
↑energy expenditure
& lipolysis
Weight maintenance/loss
CPAP
↓Sympathetic activity:
↓Energy Expenditure
↓Lipolysis
↓Leptin

Figure 3

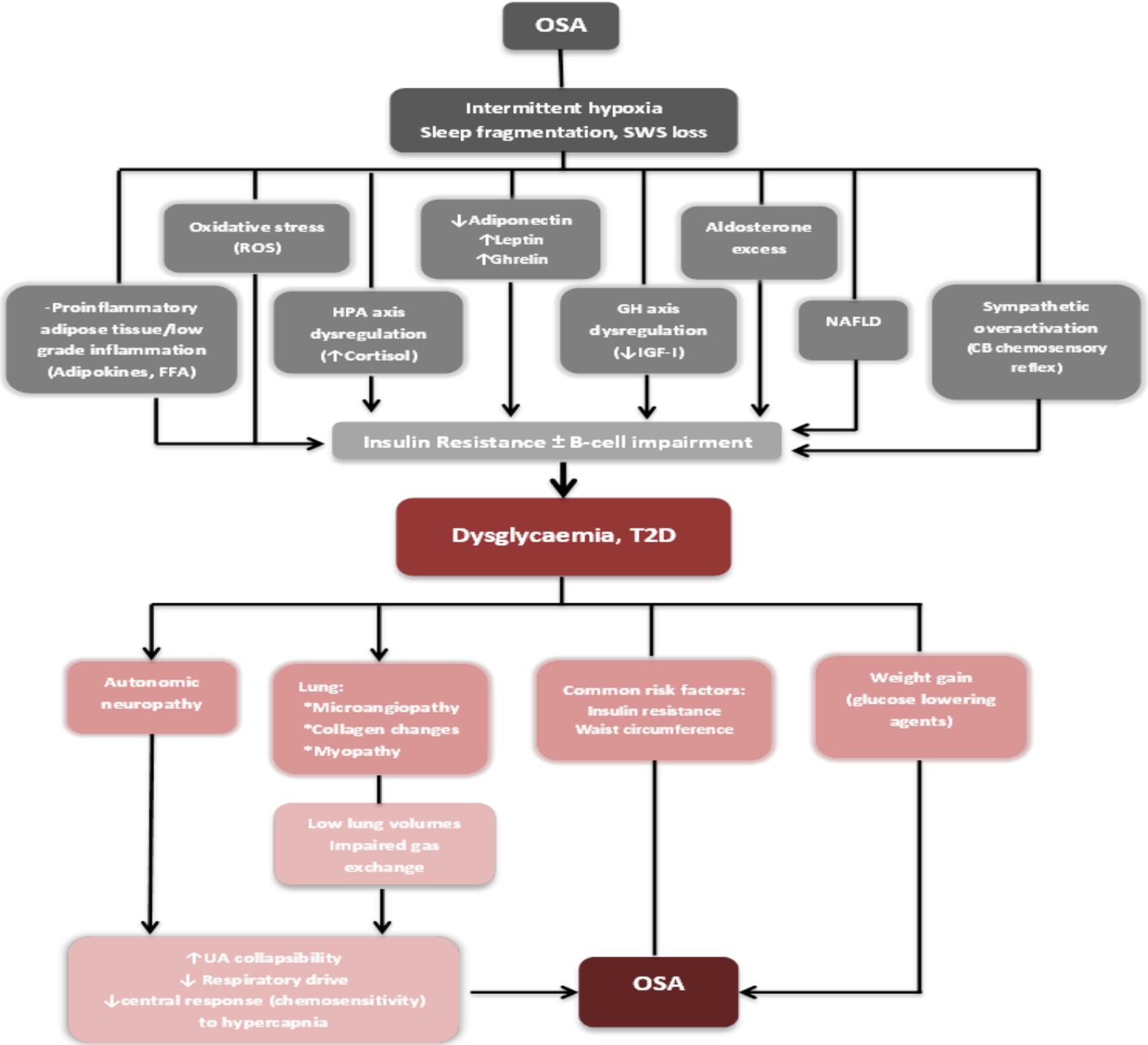

OSA
Intermittent hypoxia
Sleep fragmentation, SWS loss
Oxidative stress (ROS)
↓Adiponectin ↑Leptin ↑Ghrelin
Aldosterone excess
-Proinflammatory adipose tissue/low grade inflammation (Adipokines, FFA)
HPA axis dysregulation (↑Cortisol)
GH axis dysregulation (↓IGF-I)
NAFLD
Sympathetic overactivation (CB chemosensory reflex)
Insulin Resistance ± B-cell impairment
Dysglycaemia, T2D
Autonomic neuropathy
Lung: *Microangiopathy *Collagen changes *Myopathy
Common risk factors: Insulin resistance Waist circumference
Weight gain (glucose lowering agents)
Low lung volumes Impaired gas exchange
↑UA collapsibility ↓ Respiratory drive ↓central response (chemosensitivity) to hypercapnia
OSA

Figure 4. A

REF: **Impact of obstructive sleep apnea treatment by continuous positive airway pressure on cardiometabolic biomarkers: a systematic review from sham CPAP randomized controlled trials.** Jullian-Desayes I, Joyeux-Faure M, Tamisier R, Launois S, Borel AL, Levy P, Pepin JL. Sleep Med Rev. 2015 Jun;21:23-38. doi: 10.1016/j.smrv.2014.07.004. Epub 2014 Jul 31**.** ***(Permission needed)***

Figure 4. B

REF: Obstructive Sleep Apnoea and Type 2 Diabetes**.** Abd A Tahrani1 and Asad Ali2. *European Endocrinology*, 2014;10(1):43–50 ***(Permission needed)***

Figure 4

A.

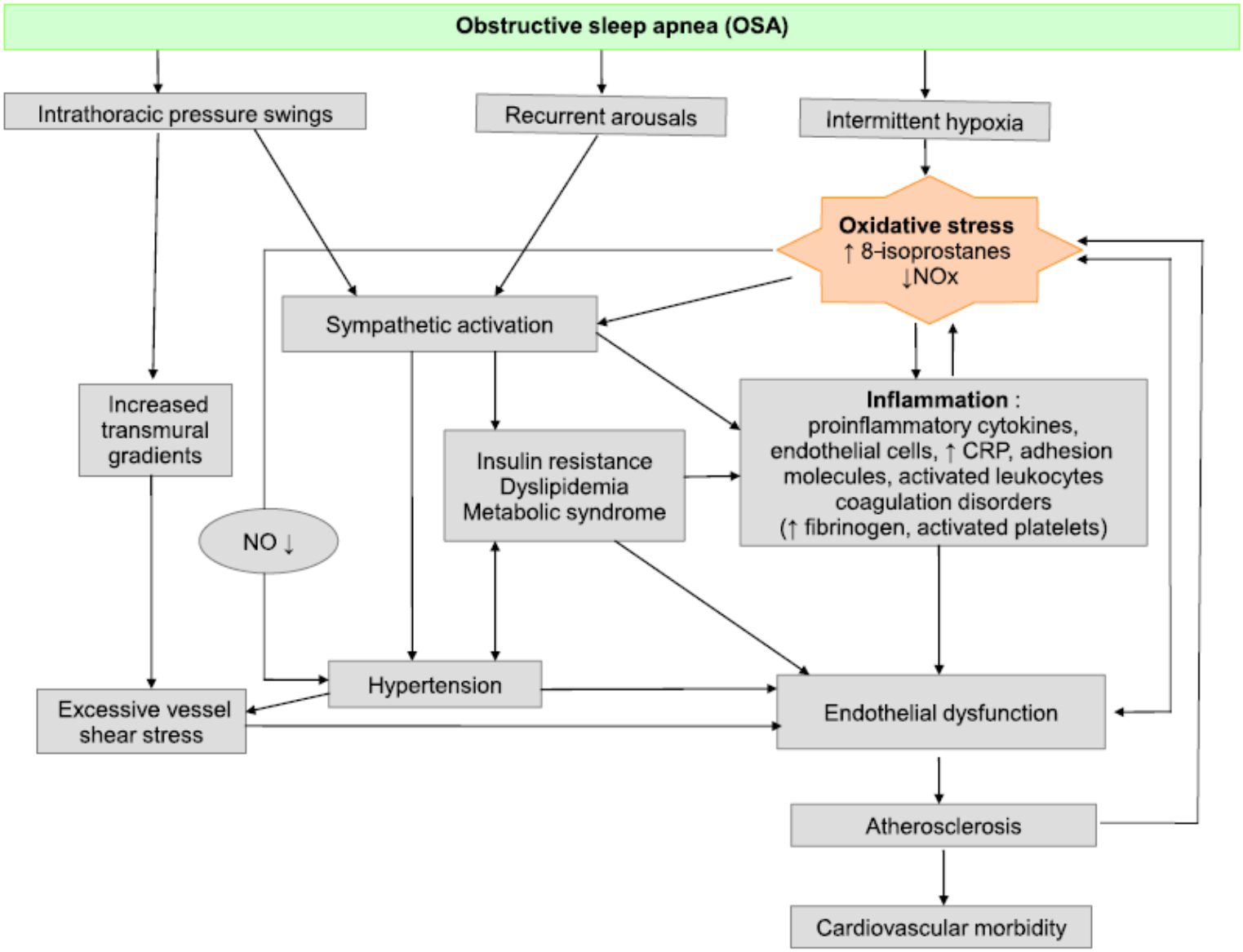

Obstructive sleep apnea (OSA)
Intrathoracic pressure swings
Recurrent arousals
Intermittent hypoxia
Oxidative stress
↑ 8-isoprostanes
↓NOx
Sympathetic activation
Increased transmural gradients
Insulin resistance
Dyslipidemia
Metabolic syndrome
Inflammation :
proinflammatory cytokines, endothelial cells, ↑ CRP, adhesion molecules, activated leukocytes
coagulation disorders
(↑ fibrinogen, activated platelets)
NO ↓
Hypertension
Excessive vessel shear stress
Endothelial dysfunction
Atherosclerosis
Cardiovascular morbidity

Figure 4

B.

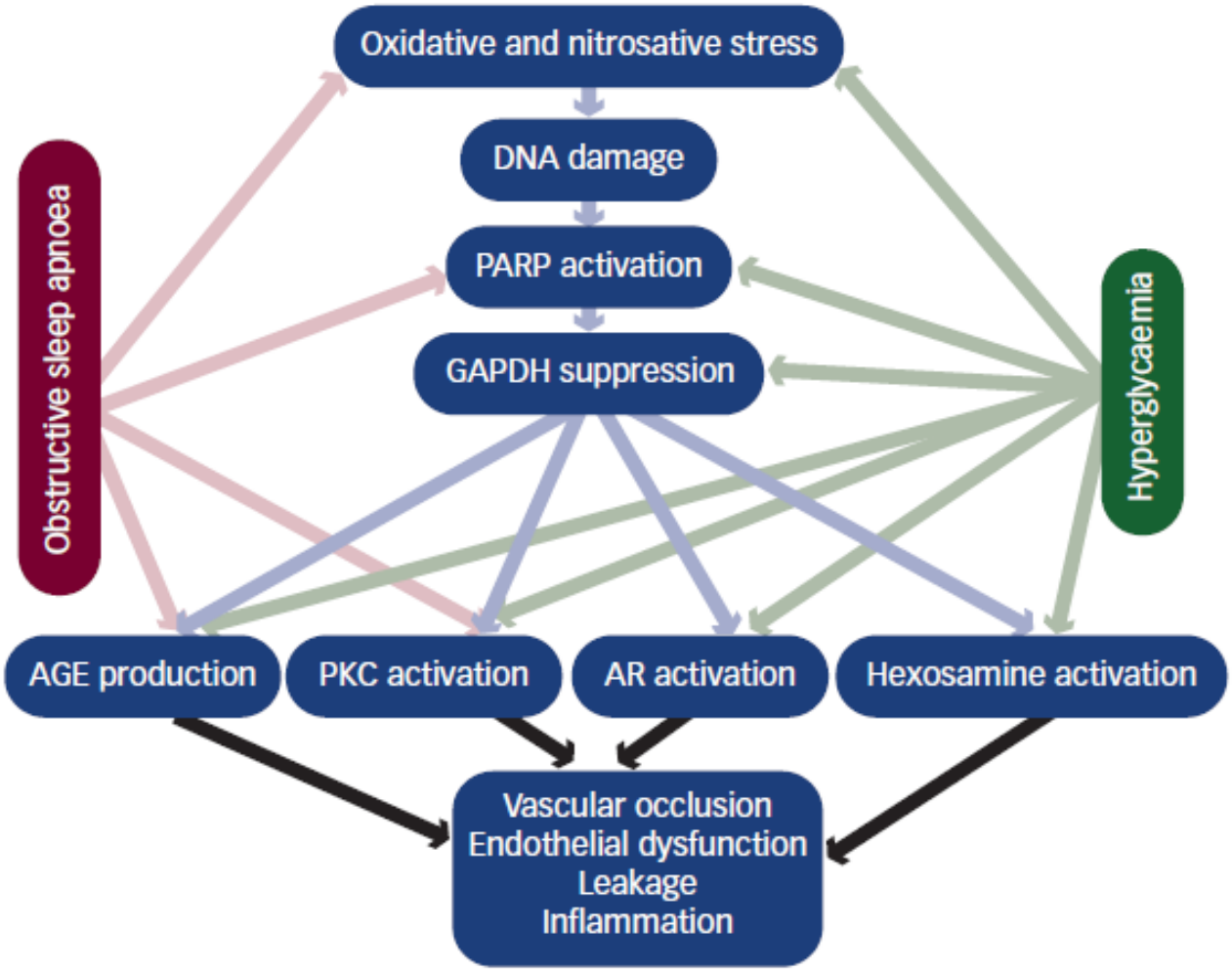

Oxidative and nitrosative stress
DNA damage
PARP activation
GAPDH suppression
Obstructive sleep apnoea
Hyperglycaemia
AGE production
PKC activation
AR activation
Hexosamine activation
Vascular occlusion
Endothelial dysfunction
Leakage
Inflammation

Figure 5

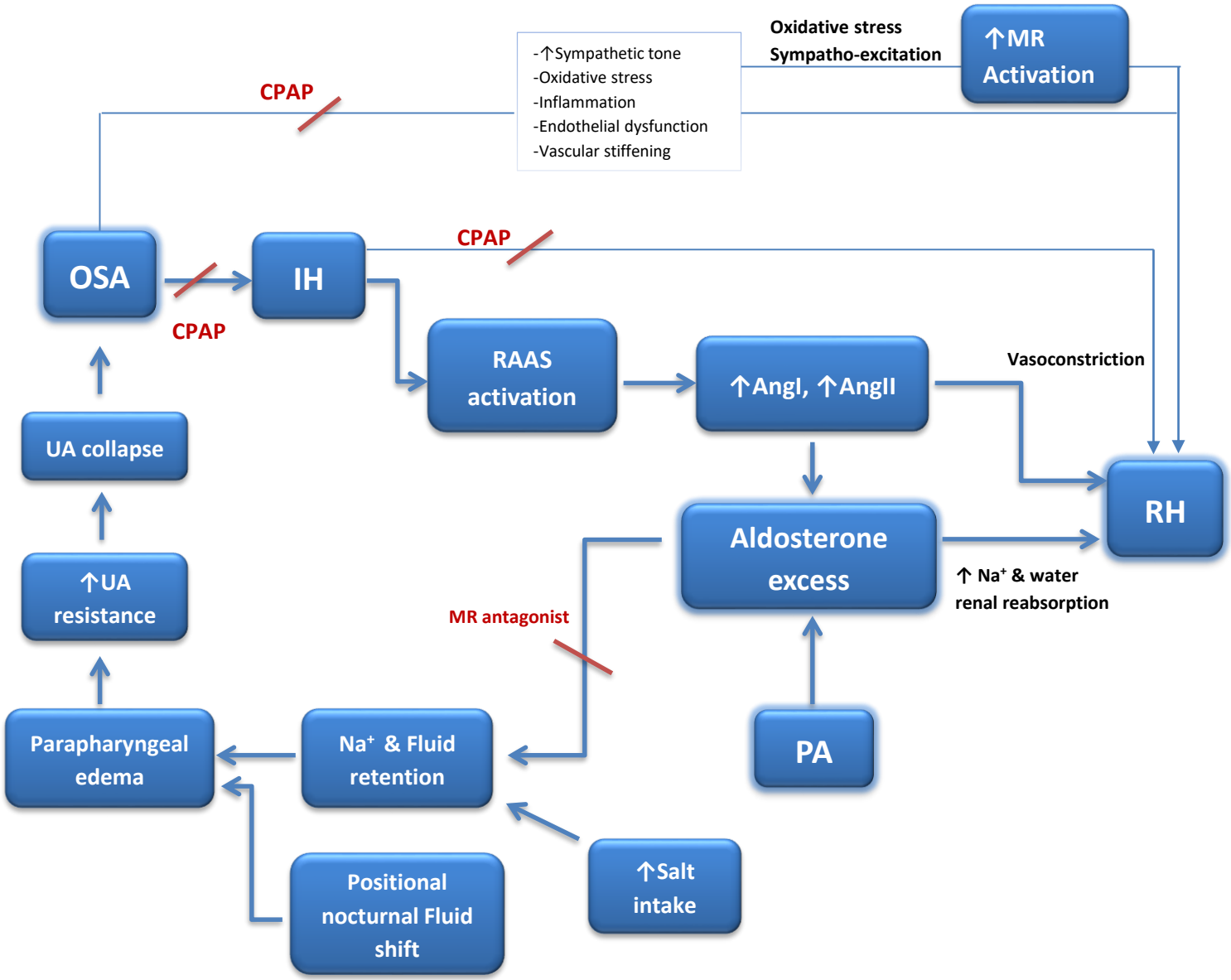

-↑Sympathetic tone
-Oxidative stress
-Inflammation
-Endothelial dysfunction
-Vascular stiffening
Oxidative stress
Sympatho-excitation
↑MR Activation
CPAP
CPAP
CPAP
OSA
IH
RAAS activation
↑AngI, ↑AngII
Vasoconstriction
RH
UA collapse
↑UA resistance
Aldosterone excess
↑ Na+ & water renal reabsorption
MR antagonist
Parapharyngeal edema
Na+ & Fluid retention
PA
Positional nocturnal Fluid shift
↑Salt intake

Figure 6

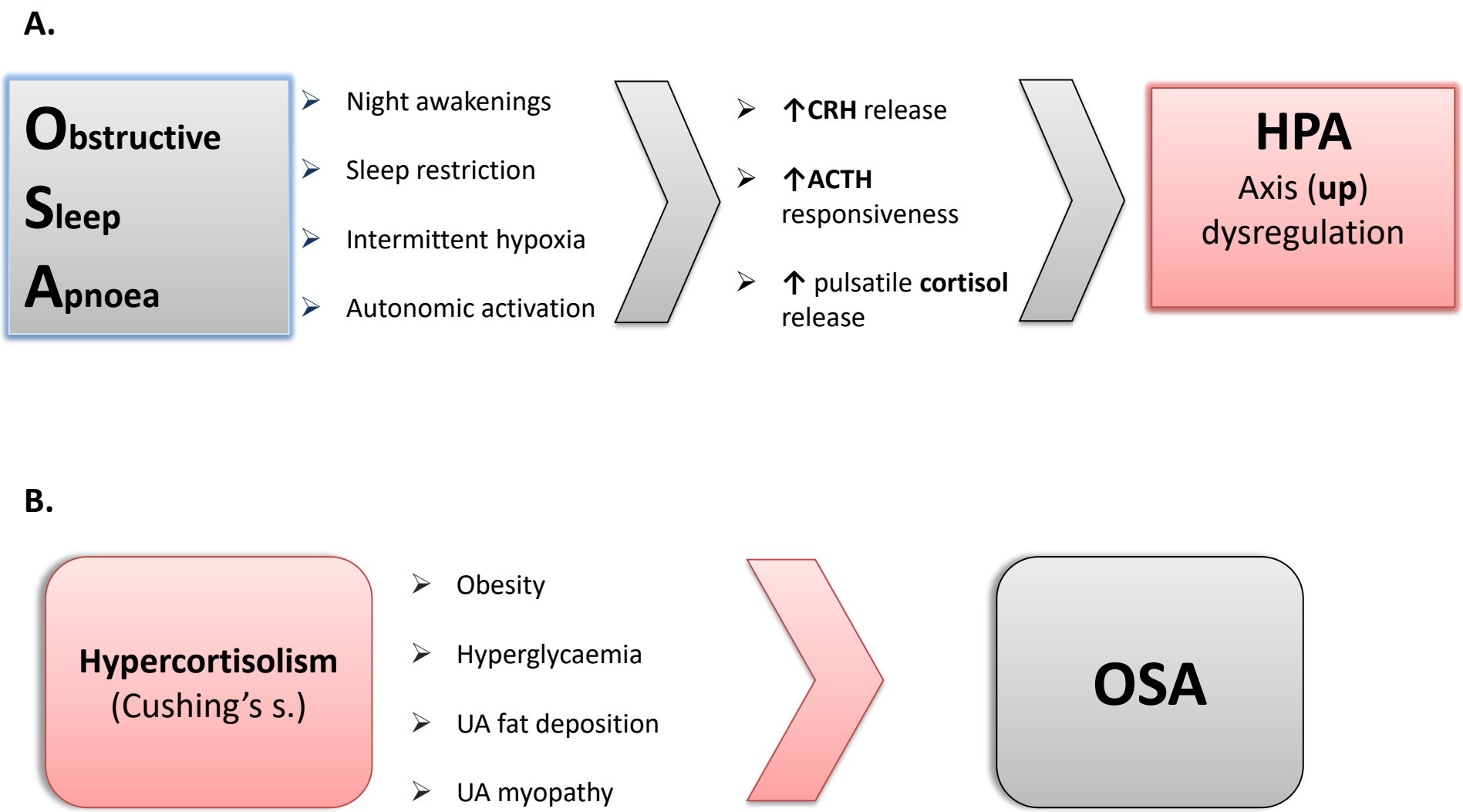

A.
Obstructive Sleep Apnoea
Night awakenings
Sleep restriction
Intermittent hypoxia
Autonomic activation
↑CRH release
↑ACTH responsiveness
↑ pulsatile cortisol release
HPA Axis (up) dysregulation
B.
Hypercortisolism (Cushing's s.)
Obesity
Hyperglycaemia
UA fat deposition
UA myopathy
OSA

Figure 7

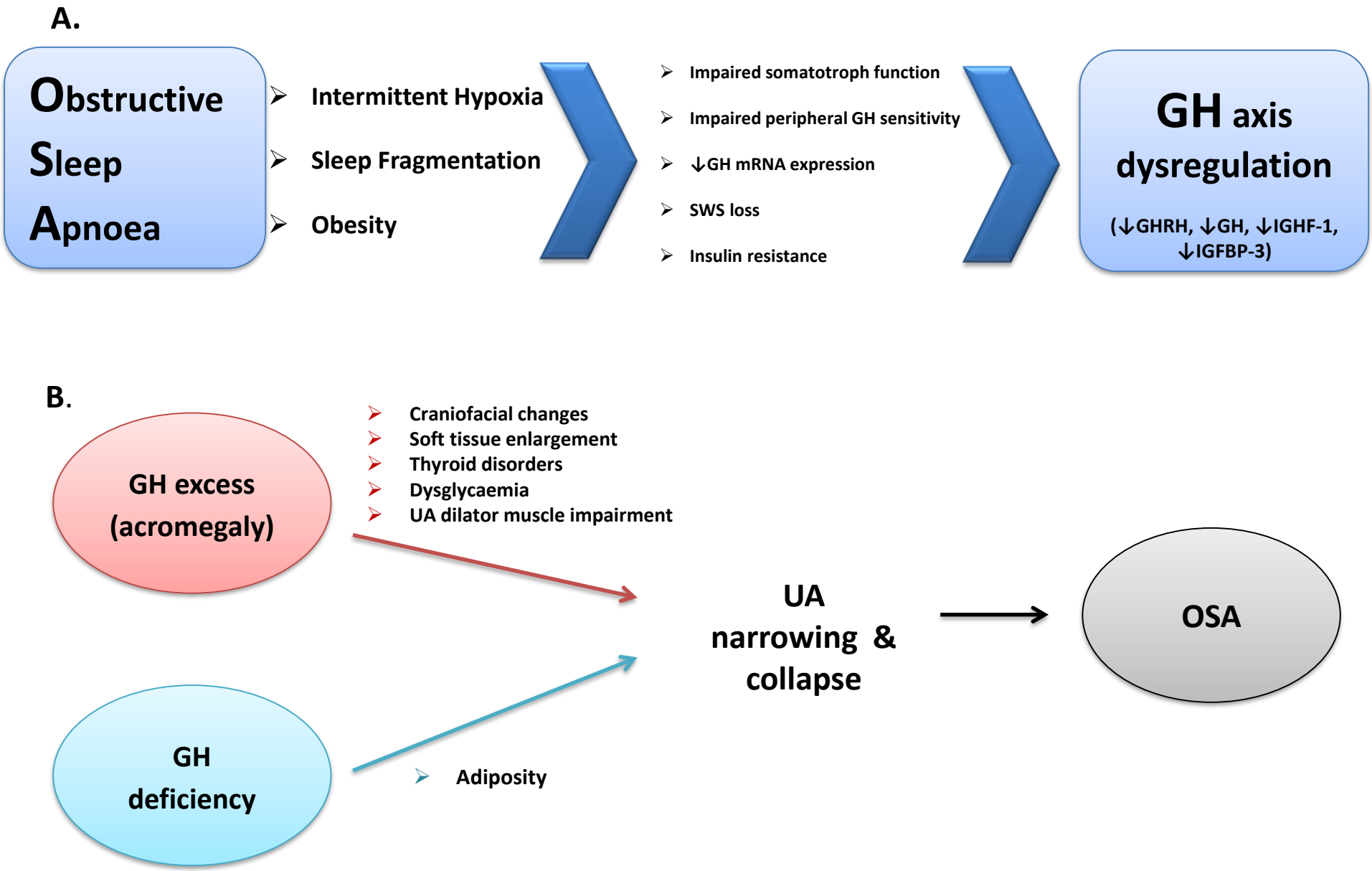

A.
Obstructive Sleep Apnoea
Intermittent Hypoxia
Sleep Fragmentation
Obesity
Impaired somatotroph function
Impaired peripheral GH sensitivity
↓GH mRNA expression
SWS loss
Insulin resistance
GH axis dysregulation
(↓GHRH, ↓GH, ↓IGHF-1, ↓IGFBP-3)
B.
GH excess (acromegaly)
Craniofacial changes
Soft tissue enlargement
Thyroid disorders
Dysglycaemia
UA dilator muscle impairment
GH deficiency
Adiposity
UA narrowing & collapse
OSA

Figure 8

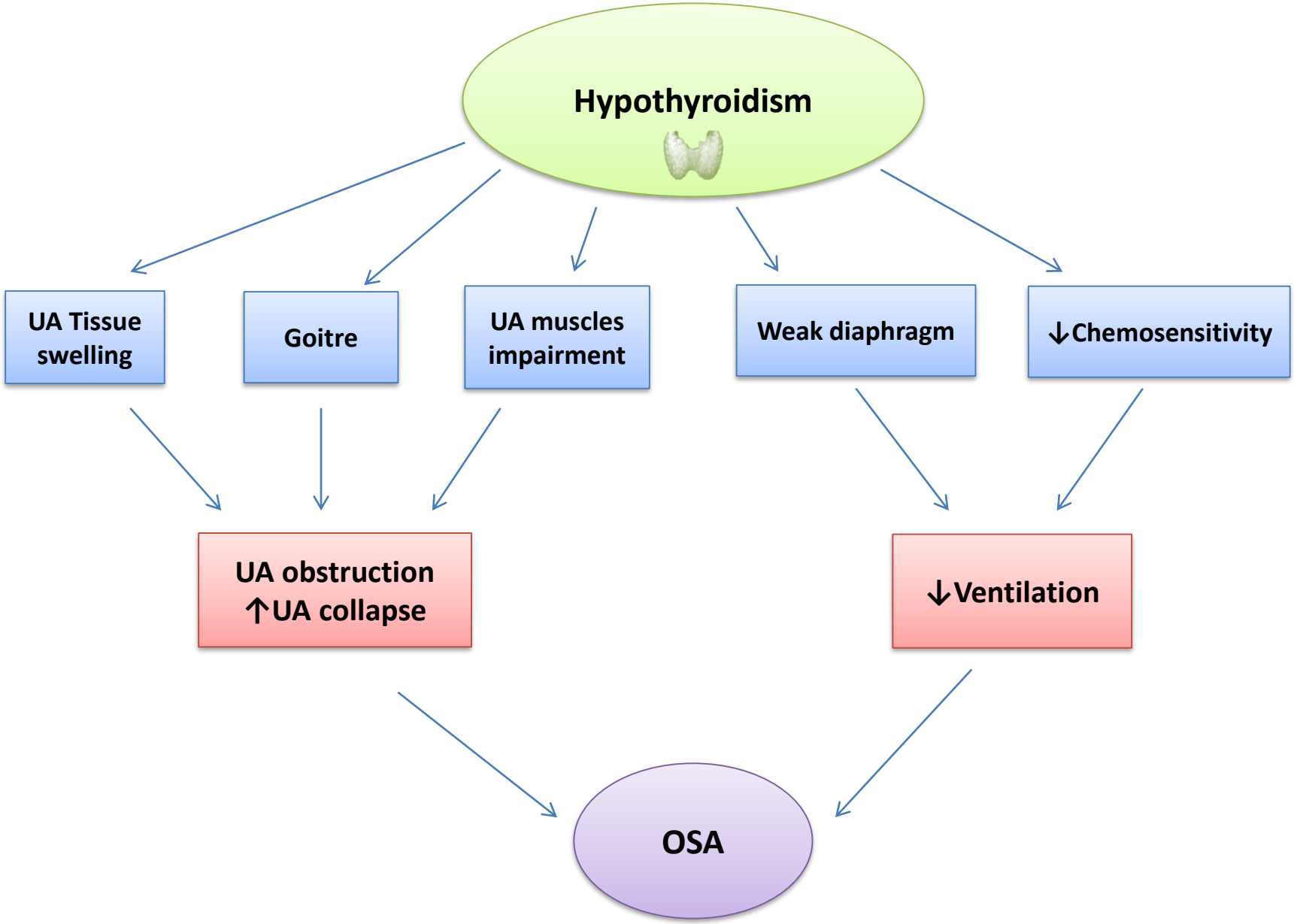
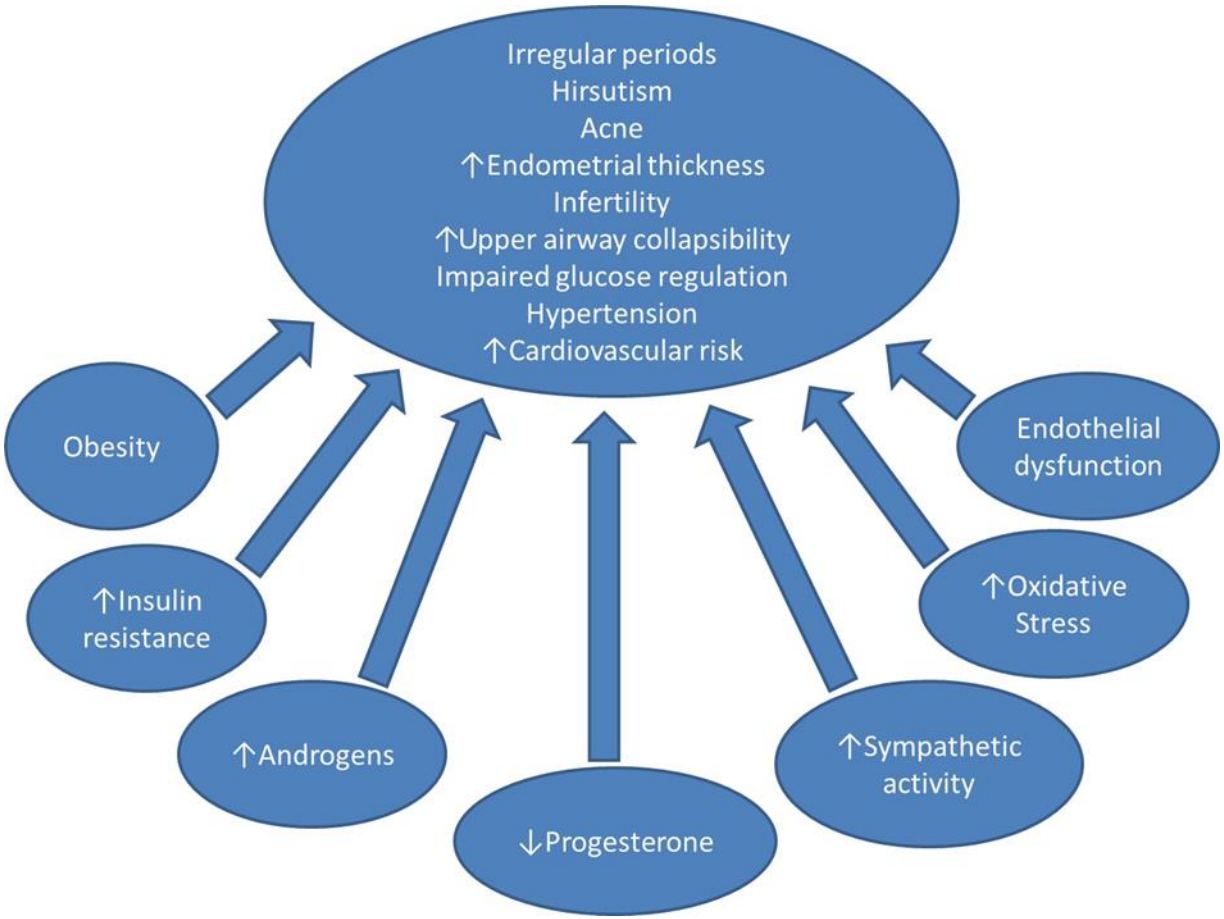
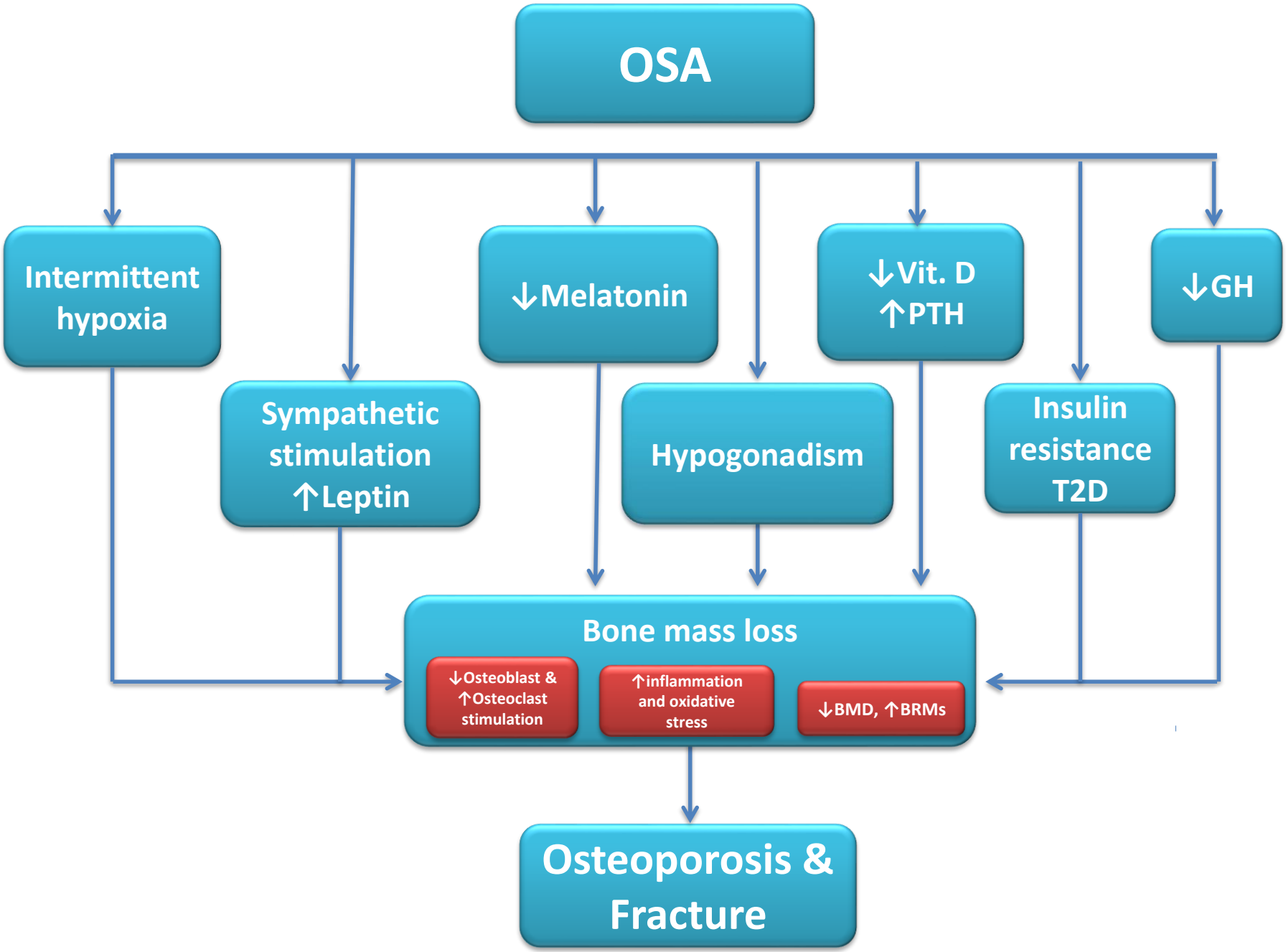

Hypothyroidism
UA Tissue swelling
Goitre
UA muscles impairment
Weak diaphragm
↓Chemosensitivity
UA obstruction ↑UA collapse
↓Ventilation
OSA

Figure 9



Ref:Hassan Kahal, Ioannis Kyrou, Abd A. Tahrani, Harpal S. Randeva . Obstructive sleep apnoea and polycystic ovary syndrome: A comprehensive review of clinical interactions and underlying pathophysiology. Clin Endocrinol (Oxf). 2017 Oct;87(4):313-319. doi: 10.1111/cen.13392. Epub 2017 Jul 14. ***(Permission needed)***

Figure 10


OSA
Intermittent hypoxia
Sympathetic stimulation ↑Leptin
↓Melatonin
Hypogonadism
↓Vit. D ↑PTH
Insulin resistance T2D
↓GH
Bone mass loss
↓Osteoblast & ↑Osteoclast stimulation
↑inflammation and oxidative stress
↓BMD, ↑BRMs
Osteoporosis & Fracture

Online Supplement

OSA overview

OSA pathogenesis

Although the upper airway (UA) consists of rigid, cartilaginous structures, its patency can be compromised along a soft segment extending from the hard palate to the larynx (the pharynx), which allows the UA to change shape for speech and swallowing during wakefulness [1-3]. However, in the presence of anatomically compromised upper airways (UAs), as in patients with OSA, the loss of wakefulness inputs to the control of the UAs and chest wall muscle motor neurons during sleep, produce UAs obstruction[4]. The underlying mechanisms driving these UAs obstructions are complex and multi factorial **(Figure 1 of the online supplement).**

Patients with OSA have narrower UAs[5, 6] with enlarged surrounding soft tissues compared to healthy controls; thus increasing the risk of collapse during sleep **(Figure 2 of the online supplement)**[7-11]. During wakefulness, the UA dilator muscles (genioglossus most studied) activity is increased in patients with OSA, compared to healthy controls, compensating for the anatomically diminished UA size; while during sleep the UA dilator muscles activity is greatly reduced leading to pharynx collapse and subsequently UA obstruction, particularly during rapid-eye-movement (REM) sleep [1, 2, 12, 13]. This reduction in UAs muscle tone during sleep is due to a combination of central lack of respiratory drive and local inhibitory reflexes that respond to changes in pressure in the UAs[1]. The chemoreceptors are also less responsive to PaO_2 and $PaCO_2$ changes during sleep[14], resulting in a reduced input to the respiratory centers in the brainstem and reduced UA dilators activity[15-17]. Even very small and transient reductions in $PaCO_2$ can result in significant apnoea due to the changes in chemoreceptors activity during sleep[4]. The reduced UA dilator muscles activity is also due to reduced mechanoreceptors' responses to changes in negative UA pressure (genioglossus negative pressure reflex[18, 19]) during REM.

Respiratory arousal threshold (RAT) also plays an important role in the pathogenesis of OSA in some patients[20]. In response to changes in gas exchange, pH, lung volumes or UAs resistance, the respiratory centres in the brainstem can increase respiratory effort, which triggers an arousal from sleep when RAT is reached[2, 21]. Hence, arousals are protective as they increase UA muscle tone (similar to the awake state) and finally open obstructed UAs[1]. However, low RAT can have detrimental effects in patients with OSA as more frequent

arousals can result in a disruption in sleep architecture and in restoring airflow before the development of adequate ventilatory drive and result in ventilatory overshoot associated with the sleep/wake transition leading to further obstructive episodes[1, 2, 20-23].

Another important element in OSA development is the ventilatory control stability, known as loop gain, which refers to the size of a "ventilatory correction" as a response to a "ventilatory disturbance"[2, 24]. Accordingly, in case of a high loop gain, small decrease in breathing will lead to a large correction. In the case of OSA, the loop gain appears to be elevated[25], suggesting high responsiveness of the ventilatory system to disturbed breathing with a propensity to develop cyclical fluctuations in breathing output and increased response to arousal by hyperventilation driving $PaCO_2$ below the apnea threshold[1, 26, 27].

There are multiple other factors that contribute further to the pathogenesis of OSA and UA collapsibility including low lung volume (resulting in lack of pharyngeal stretching), reduced UAs surface tension and UA oedema [2, 28-32].

OSA risk factors

Excess body weight is the main risk factor for OSA[33]. Weight gain of 10% is associated with a 6-fold higher risk of moderate to severe OSA development[34]. Similarly, 9% weight loss in patients with obesity and OSA results in 47% reduction in apneas frequency[35] and 60% reduction in the Apnoea- Hypopnoea index (AHI) after 17% drop in BMI[36]. Men have consistently been shown to be at a 2- to 3-fold higher risk of OSA compared to women[37]; possibly due to differences in sex hormones which will be detailed later. Multiple studies showed African-Americans to be at increased risk of OSA compared to White Caucasians[38-40]. Whereas, differences in the prevalence of OSA in Asians vs. white Caucasians were inconsistent across multiple studies[38, 41, 42]. The ethnic variations could be related to differences in UA anatomy, respiratory arousal thresholds, fat distribution, genetic and environmental factors[37, 43-45]. Prevalence of OSA increases with increasing age[33], being 2-3 fold higher in older people (≥65y), reaching eventually a plateau after the age of 65[37]. Other risk factors include smoking, excess alcohol intake, nasal obstruction and menopause[37].

OSA clinical features

Snoring is the most frequent OSA symptom symptom but it is not diagnostic for the disease, as most snorers don't have OSA and; only 6% of patients with OSA do not report snoring[46], but it is very frequent in general population as well[46]. Other clinical features include, witnessed apneas, nightly chocking and gasping (reflecting an arousal after an apnea event), insomnia, nocturia, enuresis, arousals, sweating[47], excessive daytime sleepiness (EDS), and a

variety of other daytime symptoms such as fatigue, memory loss, irritability, morning headaches, depression, and erectile dysfunction[46, 48].

OSA comorbidities and associations:

OSA is associated with significant comorbidities such as hypertension, Type 2 diabetes, cardiovascular disease, mortality, road traffic accidents, chronic kidney disease amongst others [4, 47, 49, 50].

OSA diagnosis and treatment:

Multiple definitions of OSA have been used in clinical research, which contributed to some of the variations in outcomes of studies in patients with OSA. OSA is generally diagnosed based on cut offs of parameters recorded during polysomnography or polygraphy. The AHI is defined as the average number of apnoea and hypopnea events per hour of sleep. The respiratory disturbance index (RDI) is defined as the AHI plus the respiratory-effort related arousals. The oxygen desaturation index (ODI) is the average number of oxygen desaturation per hour of sleep. The American Academy of Sleep Medicine (AASM) recommendations regarding OSA diagnosis and the criteria used to define apnoea and hypopneas are detailed here [51, 52].

Polysomnography remains the gold-standard for diagnosing OSA, although multiple portable devices have also been considered appropriate if adequate channels are recorded according to the latest AASM guidelines[52]. Sleep staging is desirable but not always considered essential. CPAP is the gold standard treatment for patients with moderate to severe OSA in addition to weight loss in patients with obesity[48, 53, 54]. Intra oral devices can be used in mild OSA and more recently upper airway stimulation can also be used in certain patients groups [55, 56].

Literature

1. Eckert DJ & Malhotra A. Pathophysiology of adult obstructive sleep apnea. *Proc Am Thorac Soc* 2008 **5** 144-153.
2. Edwards BA, Eckert DJ & Jordan AS. Obstructive sleep apnoea pathogenesis from mild to severe: Is it all the same? *Respirology* 2017 **22** 33-42.
3. Remmers JE, deGroot WJ, Sauerland EK & Anch AM. Pathogenesis of upper airway occlusion during sleep. *J Appl Physiol Respir Environ Exerc Physiol* 1978 **44** 931-938.

4. Dempsey JA, Veasey SC, Morgan BJ & O'Donnell CP. Pathophysiology of sleep apnea. *Physiol Rev* 2010 **90** 47-112.
5. Neelapu BC, Kharbanda OP, Sardana HK, Balachandran R, Sardana V, Kapoor P, Gupta A & Vasamsetti S. Craniofacial and upper airway morphology in adult obstructive sleep apnea patients: A systematic review and meta-analysis of cephalometric studies. *Sleep Med Rev* 2017 **31** 79-90.
6. Togeiro SM, Chaves CM, Jr., Palombini L, Tufik S, Hora F & Nery LE. Evaluation of the upper airway in obstructive sleep apnoea. *Indian J Med Res* 2010 **131** 230-235.
7. Schwab RJ, Pasirstein M, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G & Pack AI. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med* 2003 **168** 522-530.
8. Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, Torigian DA, Pack AI & Schwab RJ. Tongue fat and its relationship to obstructive sleep apnea. *Sleep* 2014 **37** 1639-1648.
9. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA & Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing. Significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995 **152** 1673-1689.
10. Ciscar MA, Juan G, Martinez V, Ramon M, Lloret T, Minguez J, Armengot M, Marin J & Basterra J. Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. *Eur Respir J* 2001 **17** 79-86.
11. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J & Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol (1985)* 1997 **82** 1319-1326.
12. Mezzanotte WS, Tangel DJ & White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992 **89** 1571-1579.
13. Mezzanotte WS, Tangel DJ & White DP. Influence of sleep onset on upper-airway muscle activity in apnea patients versus normal controls. *Am J Respir Crit Care Med* 1996 **153** 1880-1887.
14. Krimsky WR & Leiter JC. Physiology of breathing and respiratory control during sleep. *Semin Respir Crit Care Med* 2005 **26** 5-12.
15. Berthon-Jones M & Sullivan CE. Ventilation and arousal responses to hypercapnia in normal sleeping humans. *J Appl Physiol Respir Environ Exerc Physiol* 1984 **57** 59-67.
16. Douglas NJ, White DP, Weil JV, Pickett CK, Martin RJ, Hudgel DW & Zwillich CW. Hypoxic ventilatory response decreases during sleep in normal men. *Am Rev Respir Dis* 1982 **125** 286-289.
17. Hedemark LL & Kronenberg RS. Ventilatory and heart rate responses to hypoxia and hypercapnia during sleep in adults. *J Appl Physiol Respir Environ Exerc Physiol* 1982 **53** 307-312.
18. Pillar G, Fogel RB, Malhotra A, Beauregard J, Edwards JK, Shea SA & White DP. Genioglossal inspiratory activation: central respiratory vs mechanoreceptive influences. *Respir Physiol* 2001 **127** 23-38.
19. Horner RL, Innes JA, Murphy K & Guz A. Evidence for reflex upper airway dilator muscle activation by sudden negative airway pressure in man. *J Physiol* 1991 **436** 1529.
20. Tahrani AA. Ethnic differences in the pathogenesis of obstructive sleep apnoea: Exploring non-anatomical factors. *Respirology* 2017 **22** 847-848.

21. Jordan AS, O'Donoghue FJ, Cori JM & Trinder J. Physiology of Arousal in Obstructive Sleep Apnea and Potential Impacts for Sedative Treatment. *Am J Respir Crit Care Med* 2017 **196** 814-821.
22. Eckert DJ & Younes MK. Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol (1985)* 2014 **116** 302-313.
23. Ratnavadivel R, Chau N, Stadler D, Yeo A, McEvoy RD & Catcheside PG. Marked reduction in obstructive sleep apnea severity in slow wave sleep. *J Clin Sleep Med* 2009 **5** 519-524.
24. Khoo MC, Kronauer RE, Strohl KP & Slutsky AS. Factors inducing periodic breathing in humans: a general model. *J Appl Physiol Respir Environ Exerc Physiol* 1982 **53** 644659.
25. Salloum A, Rowley JA, Mateika JH, Chowdhuri S, Omran Q & Badr MS. Increased propensity for central apnea in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure. *Am J Respir Crit Care Med* 2010 **181** 189-193.
26. Wellman A, Jordan AS, Malhotra A, Fogel RB, Katz ES, Schory K, Edwards JK & White DP. Ventilatory control and airway anatomy in obstructive sleep apnea. *Am J Respir Crit Care Med* 2004 **170** 1225-1232.
27. Younes M, Ostrowski M, Thompson W, Leslie C & Shewchuk W. Chemical control stability in patients with obstructive sleep apnea. *Am J Respir Crit Care Med* 2001 **163** 1181-1190.
28. Jordan AS, White DP, Owens RL, Eckert DJ, Rahangdale S, Yim-Yeh S & Malhotra A. The effect of increased genioglossus activity and end-expiratory lung volume on pharyngeal collapse. *J Appl Physiol (1985)* 2010 **109** 469-475.
29. Squier SB, Patil SP, Schneider H, Kirkness JP, Smith PL & Schwartz AR. Effect of endexpiratory lung volume on upper airway collapsibility in sleeping men and women. *J Appl Physiol (1985)* 2010 **109** 977-985.
30. Kirkness JP, Madronio M, Stavrinou R, Wheatley JR & Amis TC. Relationship between surface tension of upper airway lining liquid and upper airway collapsibility during sleep in obstructive sleep apnea hypopnea syndrome. *J Appl Physiol (1985)* 2003 **95** 1761-1766.
31. Jokic R, Klimaszewski A, Mink J & Fitzpatrick MF. Surface tension forces in sleep apnea: the role of a soft tissue lubricant: a randomized double-blind, placebocontrolled trial. *Am J Respir Crit Care Med* 1998 **157** 1522-1525.
32. White LH & Bradley TD. Role of nocturnal rostral fluid shift in the pathogenesis of obstructive and central sleep apnoea. *J Physiol* 2013 **591** 1179-1193.
33. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, Hamilton GS & Dharmage SC. Prevalence of obstructive sleep apnea in the general population: A systematic review. *Sleep Med Rev* 2017 **34** 70-81.
34. Peppard PE, Young T, Palta M, Dempsey J & Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *Jama* 2000 **284** 30153021.
35. Smith PL, Gold AR, Meyers DA, Haponik EF & Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med* 1985 **103** 850-855.
36. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S & Smith PL. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991 **144** 494-498.
37. Young T, Skatrud J & Peppard PE. Risk factors for obstructive sleep apnea in adults. *Jama* 2004 **291** 2013-2016.

38. Young T, Peppard PE & Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002 **165** 1217-1239.
39. Ancoli-Israel S, Klauber MR, Stepnowsky C, Estline E, Chinn A & Fell R. Sleepdisordered breathing in African-American elderly. *Am J Respir Crit Care Med* 1995 **152** 1946-1949.
40. Redline S. Epidemiology of Sleep-Disordered Breathing. *Semin Respir Crit Care Med* 1998 **9** 113-122.
41. Amin A, Ali A, Altaf QA, Piya MK, Barnett AH, Raymond NT & Tahrani AA. Prevalence and Associations of Obstructive Sleep Apnea in South Asians and White Europeans with Type 2 Diabetes: A Cross-Sectional Study. *J Clin Sleep Med* 2017 **13** 583-589.
42. Ip MS, Lam B, Lauder IJ, Tsang KW, Chung KF, Mok YW & Lam WK. A community study of sleep-disordered breathing in middle-aged Chinese men in Hong Kong. *Chest* 2001 **119** 62-69.
43. Sakakibara H, Tong M, Matsushita K, Hirata M, Konishi Y & Suetsugu S. Cephalometric abnormalities in non-obese and obese patients with obstructive sleep apnoea. *Eur Respir J* 1999 **13** 403-410.
44. Li KK, Kushida C, Powell NB, Riley RW & Guilleminault C. Obstructive sleep apnea syndrome: a comparison between Far-East Asian and white men. *Laryngoscope* 2000 **110** 1689-1693.
45. Lee RWW, Sutherland K, Sands SA, Edwards BA, Chan TO, S SSN, Hui DS & Cistulli PA. Differences in respiratory arousal threshold in Caucasian and Chinese patients with obstructive sleep apnoea. *Respirology* 2017 **22** 1015-1021.
46. McNicholas WT. Diagnosis of obstructive sleep apnea in adults. *Proc Am Thorac Soc* 2008 **5** 154-160.
47. Tahrani AA. Obstructive sleep apnoea in diabetes: Does it matter? *Diab Vasc Dis Res* 2017 **14** 454-462.
48. Epstein et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009 **5** 263-276.
49. Tahrani AA, Ali A & Stevens MJ. Obstructive sleep apnoea and diabetes: an update. *Curr Opin Pulm Med* 2013 **19** 631-638.
50. Tahrani AA. Obstructive sleep apnoea and vascular disease in patients with type 2 diabetes. *Eur Endocrinology* 2015 **11** 581-590.
51. Berry et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med* 2012 **8** 597-619.
52. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K & Harrod CG. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. *J Clin Sleep Med* 2017 **13** 479-504.
53. Ashrafian H, Toma T, Rowland SP, Harling L, Tan A, Efthimiou E, Darzi A & Athanasiou T. Bariatric Surgery or Non-Surgical Weight Loss for Obstructive Sleep Apnoea? A Systematic Review and Comparison of Meta-analyses. *Obes Surg* 2015 **25** 12391250.
54. Hudgel DW. Critical review: CPAP and weight management of obstructive sleep apnea cardiovascular co-morbidities. *Sleep Med Rev* 2016.
55. Vanderveken OM, Beyers J, Op de Beeck S, Dieltjens M, Willemen M, Verbraecken JA, De Backer WA & Van de Heyning PH. Development of a Clinical Pathway and Technical Aspects of Upper Airway Stimulation Therapy for Obstructive Sleep Apnea. *Front Neurosci* 2017 **11** 523.

56. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA & Quinnell TG. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. *Sleep Med Rev* 2016 **27** 108-124.

Figures for the online supplement

Figure 1: Summary of the pathogenesis of obstructive sleep apnoea (OSA). $P_{crit:}$ Critical closing pressure (The pressure inside the airway at which the airway collapses); PaCO2: Partial pressure of Carbon dioxide in arterial blood

Ref: Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of Sleep Apnea. Physiol Rev 90: 47–112, 2010; doi:10.1152/physrev.00043.2008 **(Permission needed)**

Figure 2: Upper airways size in patients with OSA and healthy individuals (top); and the impact of sleep on upper airways size in a healthy individual (bottom).

A: midsagittal magnetic resonance image (MRI) in a normal subject (left) and in a patient with severe OSA (right). Highlighted are the four upper airway regions (nasopharynx, retropalatal region, retroglossal region, hypopharynx) and upper airway soft tissue (soft palate, tongue, fat) and craniofacial structures (mandible). Fat deposits are shown in white on the MRI. Note that in the apneic patient: a) the upper airway is smaller, in both the retropalatal and retroglossal region; b) the soft palate is longer and tongue size is larger; and c) the quantity of subcutaneous fat is greater. **B:** state dependence of upper airway size in a normal subject as assessed via three-dimensional reconstructions of MRI images. Images represent averages taken over several respiratory cycles during eupneic breathing in sleep and wakefulness. Airway volume during NREM sleep is smaller in the retropalatal (RP) region, not in the retroglossal (RG) region. Such images show the marked effect of sleep, per se, on the loss of upper airway muscle dilator tone and also show that the upper airway does not narrow as a homogeneous tube during sleep.

*Ref: Dempsey JA, Veasey SC, Morgan BJ, O'Donnell CP. Pathophysiology of Sleep Apnea. Physiol Rev 90: 47–112, 2010; doi:10.1152/physrev.00043.**2008 (Permission needed)***

Figure 1

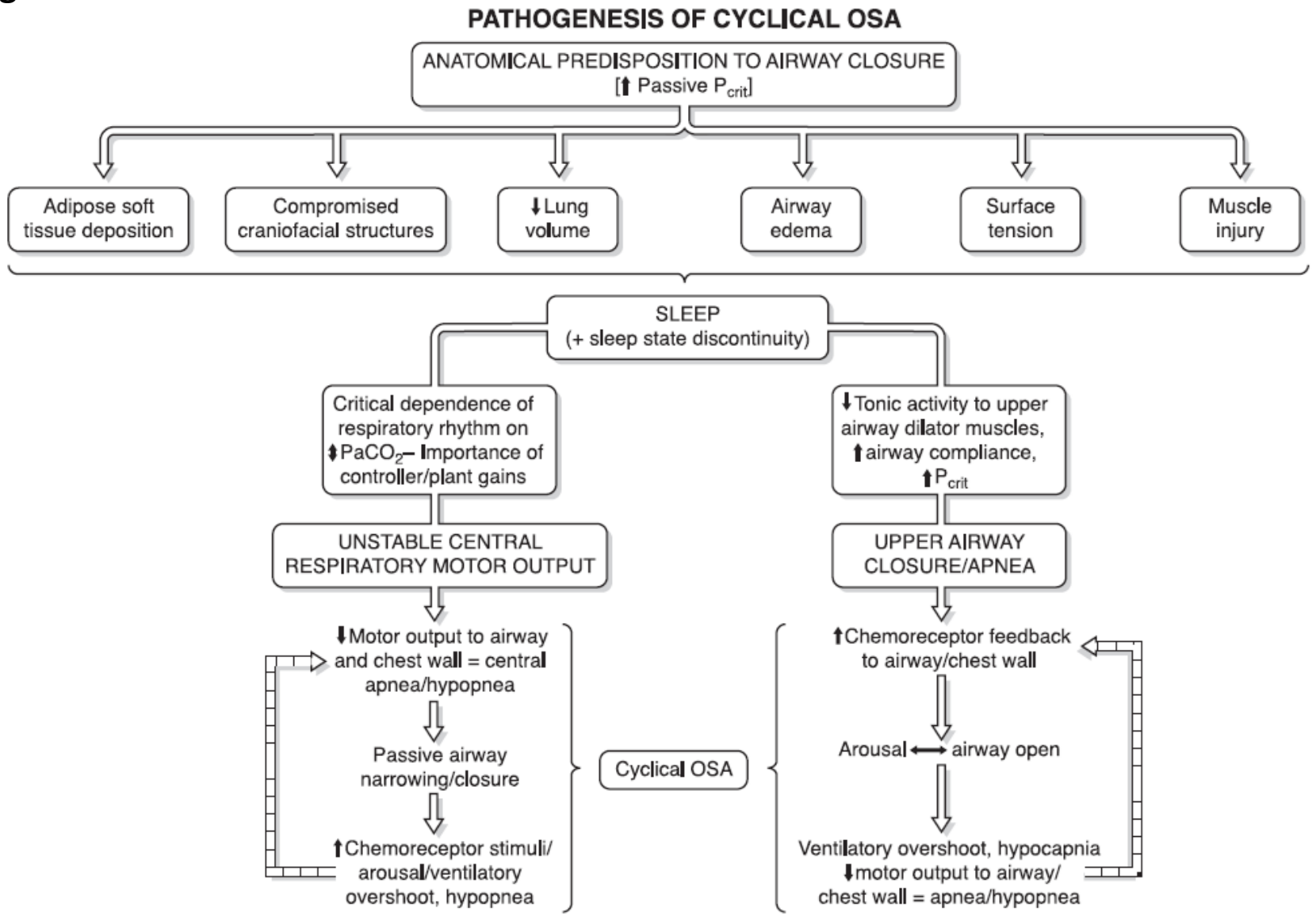
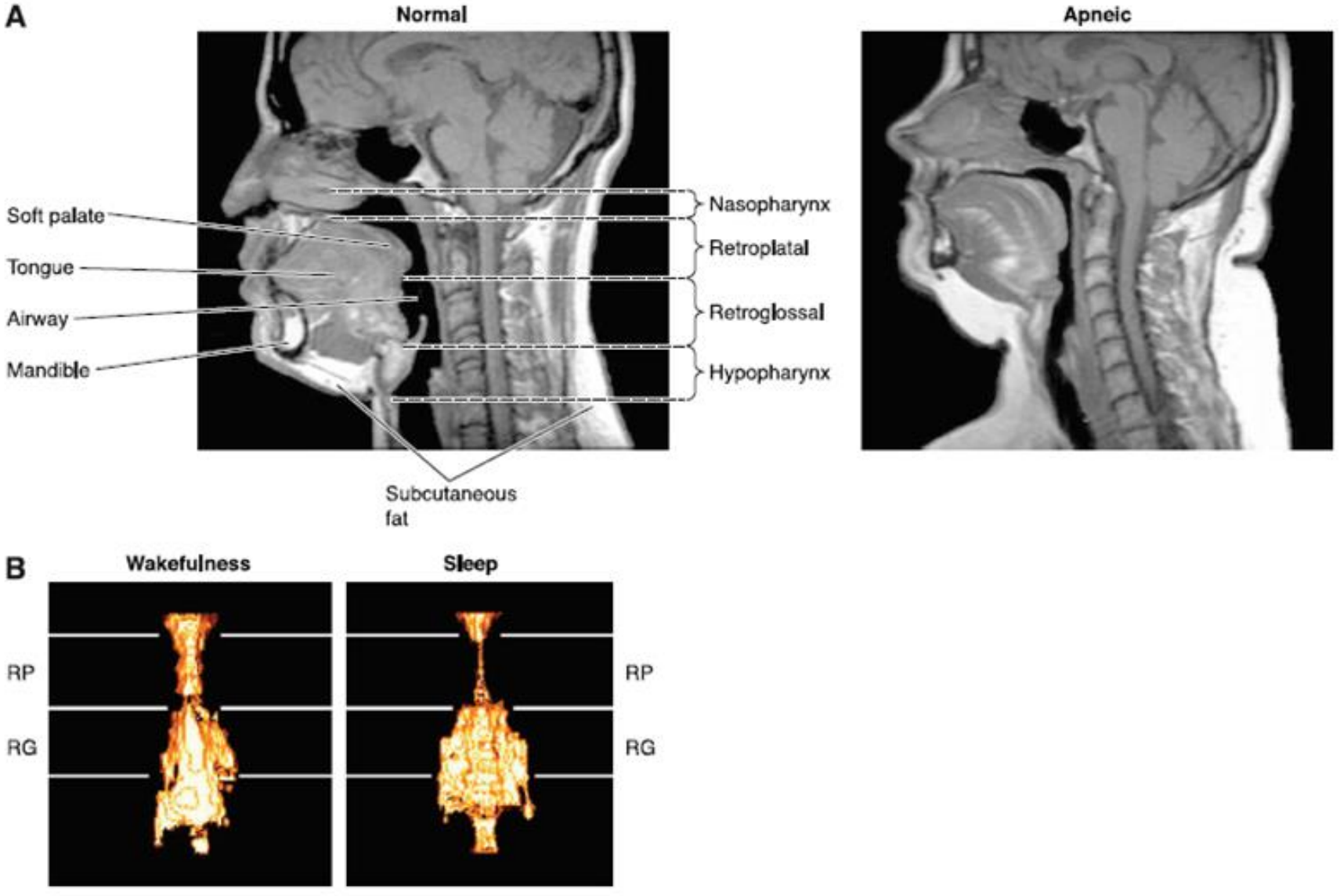

PATHOGENESIS OF CYCLICAL OSA
ANATOMICAL PREDISPOSITION TO AIRWAY CLOSURE
[⬆ Passive P_{crit}]
Adipose soft tissue deposition
Compromised craniofacial structures
⬇Lung volume
Airway edema
Surface tension
Muscle injury
SLEEP
(+ sleep state discontinuity)
Critical dependence of respiratory rhythm on ⬍⬍$PaCO_2$– Importance of controller/plant gains
⬇Tonic activity to upper airway dilator muscles, ⬆airway compliance, ⬆P_{crit}
UNSTABLE CENTRAL RESPIRATORY MOTOR OUTPUT
UPPER AIRWAY CLOSURE/APNEA
⬇Motor output to airway and chest wall = central apnea/hypopnea
Passive airway narrowing/closure
⬆Chemoreceptor stimuli/ arousal/ventilatory overshoot, hypopnea
Cyclical OSA
⬆Chemoreceptor feedback to airway/chest wall
Arousal ⟷ airway open
Ventilatory overshoot, hypocapnia
⬇motor output to airway/ chest wall = apnea/hypopnea

Figure 2


A
Normal
Apneic
Soft palate
Tongue
Airway
Mandible
Nasopharynx
Retroplatal
Retroglossal
Hypopharynx
Subcutaneous fat
B
Wakefulness
Sleep
RP
RG
RP
RG