

## Endocrine Aspects of Obstructive Sleep Apnea

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**Context:** Some endocrine and metabolic disorders are associated with a high frequency of obstructive sleep apnea (OSA), and treatment of the underlying endocrine disorder can improve and occasionally cure OSA. On the other hand, epidemiological and interventional studies suggest that OSA increases the cardiovascular risk, and a link between OSA and glucose metabolism has been suggested, via reduced sleep duration and/or quality.

**Evidence Acquisition:** We reviewed the medical literature for key articles through June 2009.

**Evidence Synthesis:** Some endocrine and metabolic conditions (obesity, acromegaly, hypothyroidism, polycystic ovary disease, etc.) can be associated with OSA. The pathophysiological mechanisms of OSA in these cases are reviewed. In rare instances, OSA may be improved or even cured by treatment of underlying endocrine disorders: this is the case of hypothyroidism and acromegaly, situations in which OSA is mainly related to upper airways narrowing due to reversible thickening of the pharyngeal walls. However, when irreversible skeletal defects and/or obesity are present, OSA may persist despite treatment of endocrine disorders and may thus require complementary therapy. This is also frequently the case in patients with obesity, even after substantial weight reduction.

**Conclusions:** Given the potential neurocognitive consequences and increased cardiovascular risk associated with OSA, specific therapy such as continuous positive airway pressure is recommended if OSA persists despite effective treatment of its potential endocrine and metabolic causes. (*J Clin Endocrinol Metab* 95: 483–495, 2010)

*"Apropos of sleep, that sinister adventure of all our nights, we might say that men go to bed daily with an audacity that would be incomprehensible if we did not know that it is the result of ignorance of the danger."*

Charles Baudelaire, in "Fusées, IX"

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent episodes of apnea or hypopnea due to total or partial pharyngeal collapse and temporary upper airway (UA) obstruction during sleep, resulting in repeated episodes of hypoxemia and hypercapnia. Frequent arousal ensures pharynx opening and restores airflow, but it fragments sleep and alters its quality. OSA associated with excessive daytime sleepiness is referred to as the OSA syndrome (OSAS). In the United States, 24% of men and 9%

of women have OSA, and 4 and 2% of middle-aged men and women, respectively, have OSAS (1, 2). Similar figures have been found in Europe and Asia (3).

OSA is pertinent to endocrinologists for at least three reasons. First, some endocrine and metabolic disorders (obesity, acromegaly, hypothyroidism, etc.) are associated with a high frequency of OSA, and treatment of the underlying endocrine disorder can improve and occasionally cure OSA. Second, epidemiological and interventional

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Abbreviations: AHI, Apnea-hypopnea index; BMI, body mass index; CPAP, continuous positive airway pressure; MRI, magnetic resonance imaging; NREM, non-REM; OSA, obstructive sleep apnea; OSAS, OSA syndrome; PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide; PaO<sub>2</sub>, partial pressure of arterial oxygen; PCOD, polycystic ovary disease; REM, rapid eye movement; UA, upper airways.

studies suggest that OSA increases the cardiovascular risk and that its treatment may reduce this risk. Finally, a link between OSA and glucose metabolism has been suggested, via reduced sleep duration and/or quality.

We reviewed the medical literature for key articles through June 2009, derived from our own experience and research plus PubMed searches of each subheading cross-referenced with OSA. We placed most emphasis on seminal studies or the most recent published work for the subheadings concerning physiology, pathophysiology, consequences of OSA, obesity, and insulin resistance; we tried to be more exhaustive in the subheadings concerning acromegaly and hormone deficiencies.

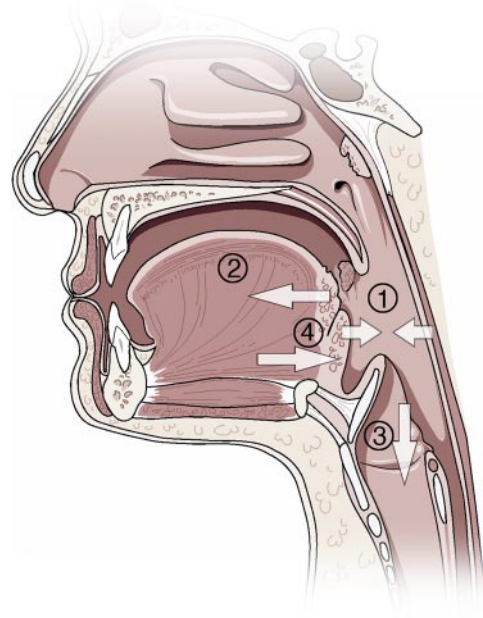
### Physiology of UA Opening during Sleep

Breathing is automatically regulated during sleep by brainstem centers that control respiratory muscle activity. As during wakefulness, the controllers respond to  $O_2$  requirements and  $CO_2$  buildup, ensuring partial pressure of arterial oxygen ( $PaO_2$ ) and partial pressure of arterial carbon-dioxide ( $PaCO_2$ ) and pH homeostasis.

#### The importance of pharyngeal dilator muscles during inspiration

Cartilaginous structures provide the airways with most of their rigidity and prevent their collapse. Only the pharynx, a soft part of the upper UA, can collapse during inspiration. Indeed, during inspiration the pharynx walls are submitted to forces (Fig. 1) that tend to push them inside the airways (4). Two mechanisms help prevent this phenomenon. First, the tonic and/or phasic activity of pharyngeal dilator muscles, composed of 10 pairs of striated muscles, contribute to rigidifying and opening the pharynx (5). These muscles are controlled by brainstem respiratory centers but can also respond directly to stimuli provided by local mechanical receptors (6). Second, longitudinal traction of the airways, which increases with tidal volume, passively contributes to rigidifying the pharynx (7).

Pharyngeal patency during inspiration seems to be the weak point during the sleep cycle. The cross-sectional area of the pharynx is reduced at various levels (8) during non-rapid eye movement (NREM) sleep and even more so during rapid eye movement (REM) sleep. UA resistance, as measured from pressure-flow loops, increases to a similar extent during NREM and REM sleep (9). Pharyngeal compliance, as determined from the cross-sectional area and pharyngeal pressure at the same level during the respiratory cycle, is increased only during REM sleep (8).



**FIG. 1.** Sagittal representation of the pharynx. Inspiration produces a collapse of pharyngeal walls due to negative pressure (1). The forces that help fight against this phenomenon and allow pharynx to remain open are the tonic and phasic contractile activity of the dilator muscles of the pharynx (2) and the longitudinal traction of the airways, which increases with the tidal volume (3). Infiltration of the tongue and/or of the pharyngeal walls and anatomic changes contribute to close the pharynx (4) and to promote OSA.

#### Control of pharyngeal dilator muscle activity involves both chemoreceptors and mechanoreceptors

The respiratory centers that control UA dilator muscle activity receive input from central and peripheral sensors. The most important of these are chemoreceptors, which seem to provide the main (or even the sole) input to the respiratory centers during sleep. They are sensitive to falls in peripheral  $PaO_2$  and to variations in  $PaCO_2$ .

Chemoreceptor responsiveness is reduced during sleep (10). More specifically, responsiveness to  $PaCO_2$  elevations is reduced during REM sleep (11), whereas responsiveness to a decline in  $PaO_2$  is reduced during both NREM and REM sleep (12). By contrast, central chemoreceptors remain highly responsive to declines in  $PaCO_2$  (inhibitor input), particularly during NREM sleep. Sleep unmasks a highly sensitive apneic threshold. Because of the exclusive chemical input to the central controller during sleep, hypocapnia seems to be critical for the onset of central apnea (13).

During NREM sleep, tonic or phasic activity of the geniohyoid muscle, a UA dilator muscle, decreases (14–16). During REM sleep the phasic activity of some UA dilator muscles has also been found to decline (15–17).

UA dilator muscle activity is also controlled by pharyngeal mechanoreceptors (18). These are very potent me-

diators of the so-called negative pressure reflex, which stabilizes the UA during inspiration. This reflex is reduced during both REM and NREM sleep (19–21).

Thus, even healthy subjects have an increased risk of apnea and hypopnea during sleep, due to the decrease in the chemical and mechanical responsiveness of dilatory UA muscles, and a few obstructive events (fewer than five episodes of apnea-hypopnea per hour of sleep) may thus be considered normal (22).

## Pathophysiology of UA Obstruction

### The different degrees of UA obstruction and their clinical impact

The first degree is simple snoring, which is due to substantial but incomplete obstruction of the UA, resulting in turbulent flow. The soft palate, particularly, flutters and is responsible for the snoring sound. An inspiratory flow limitation is seen on the pressure-flow loop, despite increasingly negative intraluminal pressure. Ventilation and gas exchanges are not perturbed, and sleep quality is normal.

The second degree of UA obstruction is the “UA resistance syndrome” (23), where UA resistance is significantly augmented and numerous episodes of inspiratory flow limitation occur. This leads to an abnormal increase in respiratory efforts during sleep and thus to the short arousals necessary to restore normal breathing. These short arousals are usually ignored in sleep analyses, but their impact is nonetheless significant because fragmented sleep can cause excessive daytime drowsiness. Snoring is frequently associated with this syndrome but is neither sufficient nor necessary for its diagnosis.

The last degree of UA obstruction is a more pronounced impairment of ventilation with, at its maximum, episodes of apnea that can be recorded by polysomnography. Interruption of breathing by complete collapse of the pharynx for at least 10 sec defines an episode of sleep apnea; a reduction in inspiratory flow of at least 50% for at least 10 sec, or inducing at least a 4% fall in oxygen saturation, defines an episode of hypopnea. The occurrence of at least five episodes of apnea-hypopnea per sleep hour defines OSA (22). The severity of OSA is measured in terms of the apnea-hypopnea index (AHI). AHI values of 5–15, 15–30, and more than 30 define mild, moderate, and severe OSA, respectively. The American Academy of Sleep Medicine classification of OSA severity takes into account both the AHI and the degree of daytime sleepiness (24). However, these thresholds are clearly arbitrary: the AHI correlates poorly with symptom severity, and the importance of excessive daytime sleepiness, especially with regard to the cardiovascular risk, is controversial (25–27).

### The pharynx as the main site of UA obstruction

Occlusion of the pharynx results from an imbalance between these two opposing forces and can thus be due to

increased positive extraluminal or negative intraluminal pressure, and/or to reduced pharyngeal dilator muscle activity, owing to intrinsic weakness or inappropriate control (Fig. 1). All these conditions may act alone or in concert, but none of them seems to be crucial for OSA to occur (28).

The determinants of surrounding extraluminal pressure include larger-than-normal tissue structures (large adenoids or tonsils, tongue hypertrophy), intraluminally displaced normal tissue (back moved tongue in retrognathia), and the presence of abnormal tissue (fat deposits, tumors, infiltration, *etc.*). Because the caliber of the pharyngeal lumen is reduced in such cases, stronger negative pressure is needed in the UA for adequate air inflow (27).

The intrinsic properties of the airway are determined both “passively,” by pharyngeal collapsibility, and “actively” by pharyngeal dilator muscle activity.

Collapsibility is estimated by measuring the critical closing pressure ( $P_{\text{CRIT}}$ ), which is the nasal pressure (normally negative) needed to obtain complete UA obstruction (29). In patients with OSA,  $P_{\text{CRIT}}$  is positive, meaning that their UA collapses at atmospheric pressure (30). Longitudinal UA tension markedly reduces the collapsibility of the pharynx. A decrease in pulmonary volume reduces longitudinal UA tension and, consequently, makes the UA more collapsible (31, 32). This effect is even more pronounced in OSAS patients (33).

### Decline in pharyngeal dilator muscle efficiency during sleep

By their tonic or phasic activity during inspiration, the pharyngeal dilator muscles are the only force preventing pharynx collapse. During wakefulness, increased pharyngeal dilator muscle activity in patients with apnea compensates for diminished airway size, thus maintaining patency (34). This neuromuscular compensation is lost during sleep in such patients, leading to airway collapse. OSA patients have a larger-than-normal fall in UA muscle activity (35), and arousals thus have a protective effect (4). Alternation between arousals that fully open the UA and sleep periods with UA obstruction may destabilize ventilatory control (36). Periodic breathing may occur, and complete or partial UA obstruction may be seen at the nadir of the ventilatory cycle (9).

Pharyngeal neuropathy or myopathy, either primary or secondary to local injury (37) or fatigue (38), may participate in some cases (39, 40).

### Diagnostic Procedures for the Approach to Patients with OSA

The gold standard for the diagnosis of OSA is still the polysomnography performed in a sleep laboratory. Clin-

ical subjective suspicion based on history record (snoring, sleep-pattern variation, excessive daytime sleepiness, and fatigue) eventually completed by a questionnaire and physical examination are obviously insufficient (41, 42). The home-based portable monitoring, which is a simpler method, is increasingly used in practice; only cardiopulmonary studies (that measure airflow, respiratory effort, electrocardiography, oxygen arterial saturation) can be recommended for the diagnosis of OSA in conjunction with a comprehensive sleep evaluation (43). The nocturnal oximetry alone has a poor diagnostic sensitivity and is not useful for evaluating the severity of OSA (44).

UA is assessed clinically and by fiber optic procedure (Muller's maneuver) to determine the level of pharyngeal collapsus (45), but its reliability is questionable (46). It must be kept in mind that these procedures are performed in a patient awake. Videendoscopy under sedation may be proposed but does not allow evaluation of the totality of UA (47). Measurement of pharyngeal pressure during sleep by a small catheter inserted in the pharynx has not proved to be useful in practice (48).

## Consequences of OSA

### Neurocognitive consequences of OSA

Neurocognitive disorders may result from frequent arousals from sleep. The increasing but insufficient efforts to correct hypoxia and hypercapnia trigger the arousals (49). Owing to this fragmented and nonrefreshing sleep, patients may suffer from daytime sleepiness, slow reactions, poor memory and concentration, irritability, and even a reduction in quality of life (3, 27). There is also an increased risk of road accidents (50) and of secondary depression (51). The Epworth Sleepiness Scale can help to document the degree of excessive daytime sleepiness (52). Treatment of OSA with continuous positive airway pressure (CPAP) can improve these neurocognitive disorders (27, 53).

### Cardiovascular consequences of OSA

OSA patients have a higher cardiovascular mortality rate (54). The risk of cardiovascular disease is increased even by mild OSAS (55).

Hypertension frequently accompanies OSA, as shown in cross-sectional studies (reviewed in Ref. 25). In a prospective study, compared with an AHI of zero, an AHI of more than 15 was associated with an almost 3-fold risk of developing hypertension (56). OSA may be particularly prevalent in drug-resistant hypertension and is associated with elevated levels of plasma aldosterone (57). Hyper-

tension in these patients is likely due to an increase in sympathetic tone and a reduction in vagal tone (elicited by a reduction in PaO<sub>2</sub> and an increase in PaCO<sub>2</sub> during episodic cessation of breathing, but also by frequent arousals) and to the more negative intrathoracic pressure, which contributes to increasing cardiac preload and left ventricular afterload. Moreover, hypoxia promotes the formation of reactive oxygen species, potentially resulting in oxidative stress, inflammation, endothelial dysfunction, and increasing blood pressure (58, 59). These mechanisms probably also explain the increased risk of atherosclerosis in patients with OSA (58, 60).

Significant independent links between OSA and coronary heart disease, arrhythmias, heart failure, and stroke have been observed in epidemiological studies. Randomized trials of CPAP have shown a modest lowering of blood pressure (particularly in hypertensive patients with more severe apnea and excessive daytime somnolence), improved left ventricular systolic function, and reduced sympathetic activity in patients with heart failure, and fewer ventricular premature beats (reviewed in Ref. 25). However, large randomized trials are needed to show definitively whether treating OSA (particularly forms without excessive daytime sleepiness) improves cardiovascular status (61).

### Effects of OSA on hormonal axes

OSA may have consequences on hormonal axes (reviewed in Ref. 62).

Variable degrees of hypogonadism are associated with OSA. This impairment of pituitary-gonadal axis (63, 64) is linked to the degree of hypoxia and disordered breathing, independently of increasing age or obesity (65). In male patients, hypogonadism improves with CPAP (66) and in female patients higher AHI is associated with lower serum estradiol and progesterone (67), suggesting that OSA may also be associated with impaired ovarian function.

OSA is also associated with hypoxia-induced sympathetic activation, which may contribute to hypertension via the stimulation of renin-angiotensin-aldosterone system (see *Cardiovascular consequences of OSA*). However, results of studies measuring the levels of renin, angiotensin II, or aldosterone in patients with OSA and the effects of CPAP are conflicting (66, 68, 69).

By contrast, no clear involvement of hypothalamic-pituitary-adrenal axis was demonstrated in patients with OSA except for an exaggerated response of ACTH to CRH, not explained by obesity alone (66, 70).

No dysfunction of hypothalamo-pituitary-thyroid axis has been found in patients with OSA (70).

## Obesity and OSA

OSA is a major complication of obesity. Severely obese subjects (candidates for bariatric surgery) have a prevalence of OSA of between 55 and 100% (71, 72). However, the risk is not limited to severe obesity because even moderate weight gain is associated with an increased risk of sleep apnea: relative to stable weight, 10% weight gain was associated with an approximate 32% increase in the AHI (73). Fat distribution is of particular importance: neck circumference (indicative of fat deposition around the UA) was found to be a better predictor of OSA than body mass index (BMI) (74). The pathophysiology of OSA in obesity is multifactorial. Fat deposits in the lateral wall of the pharynx reduce the caliber of the UAs (75) and increase their collapsibility (76). The reduced caliber of the UA in obesity is due more to the increased thickness of the lateral pharyngeal muscle wall (77) than to parapharyngeal fat pads. Moreover, the UA dilator muscles, and notably the genioglossus, are mechanically impaired and more fatigable in obese patients (78). Abdominal fat deposition reduces pulmonary volume, leading to a decrease in longitudinal UA tension and to a more collapsible UA (79). Some authors have found that waist circumference is a better predictor of sleep apnea than is neck circumference or BMI, inferring that the link between obesity and sleep apnea cannot be explained solely by neck fat deposition but may also be related to visceral obesity (80) and insulin resistance (81). The metabolic syndrome, which is up to nine times more prevalent in subjects with OSA, aggravates the cardiovascular consequences of OSA via an increase in proinflammatory cytokines IL-6 and TNF- $\alpha$ , independently of obesity (82).

Weight loss improves OSA but seems unable to cure it (83). In a recent meta-analysis of the effects of bariatric surgery on OSA, the pooled baseline AHI of 54.7 events per hour was reduced to a final value of 15.8 events per hour, consistent with moderately severe OSA (84). After an initial improvement associated with weight loss, AHI may gradually recur, even without weight regain (85). This suggests that patients should not expect OSA to be cured by surgical weight loss and that most will need to continue treatment for OSA (such as CPAP) to minimize its complications. In fact, fat loss probably varies from one site to another in these massively obese patients when they lose weight, and persisting cervical fat deposition or abnormal UA collapsibility may explain how these patients keep OSA. Finally, the presence of OSA needs to be taken into account in the decision of bariatric surgery because the perioperative risk of death or adverse outcome increases with a diagnosis of OSA (86).

Links between OSA and the metabolic syndrome, independently of obesity, are a complicated issue (62, 87), as illustrated by the fact that effective OSA treatment with CPAP does not seem to improve the metabolic syndrome in obese patients (88), whereas it reduces visceral fat in nonobese patients (89).

## Insulin Resistance, Altered Glucose Metabolism, and OSA

### Diabetes mellitus and altered glucose metabolism

Epidemiological studies suggest a link between OSA severity and the risk of type 2 diabetes mellitus, independently of obesity (90–92). However, the majority of these studies were cross-sectional (which limits evidence of causality), and OSA severity was not always assessed by polysomnography: some studies used only snoring as a marker of OSA (reviewed in Ref. 93). One explanation for this link, which is also supported by experimental data, is that OSA may affect glucose tolerance; but an alternative explanation is that diabetes mellitus might itself result in OSA by altering breath control during sleep, via autonomic neuropathy for example.

Data on insulin resistance in patients with OSA are conflicting (93). Moreover, most relevant studies used BMI rather than measures of visceral fat (such as waist circumference) to adjust for adiposity. Thus, it is unclear whether OSA itself, independently of adiposity (particularly visceral fat), predisposes individuals to diabetes mellitus.

Results of studies of the effects of CPAP treatment of OSA are also conflicting (93), even if some data strongly suggest an effect of CPAP on visceral fat (89). The only randomized study, involving patients with type 2 diabetes and OSA who were treated for 3 months with true or sham CPAP, showed no effect of CPAP on glycosylated hemoglobin or insulin resistance (94).

The main mechanism linking OSA to altered glucose metabolism, more than intermittent hypoxia, may be the neuroendocrine consequences of sleep fragmentation (93, 95), a view supported by abundant experimental and epidemiological data. In animal model, intermittent hypoxia induces a chemoreceptor sympathetic activation that may have consequences on glucose metabolism but is also able to directly reduce insulin sensitivity (96); data in humans are more speculative. Increased oxidative stress, with its consequences on nitric oxide bioavailability, increased lipid peroxidation, and up-regulation of nuclear factor- $\kappa$ B and hypoxia-inducible factor-1, is probably the main determinant of the insulin resistance induced by hypoxia (97).

More importantly, OSA is associated with a reduction in total sleep time and with sleep fragmentation. Even in

the absence of breathing disturbances, these sleep disturbances can affect glucose tolerance as shown by several epidemiological studies (reviewed in Refs. 93 and 98). In experimental studies, restricting sleep duration has an impact on glucose tolerance by a direct effect on insulin sensitivity (99, 100), but also on appetite (101). Sleep fragmentation with induction of low levels of slow-wave sleep is associated with an elevation of sympathetic nervous activity, which in turn could lead to alterations in glucose metabolism (98, 102).

Whether or not OSA is associated with more severe diabetic complications or mortality has not been studied extensively in diabetic patients but is likely in the context of increased cardiovascular risk of these patients (see *Cardiovascular consequences of OSA*). In practical terms, systematic evaluation of the risk of OSA in patients with type 2 diabetes may be recommended because the treatment of potential OSA may help to manage diabetes and other cardiovascular risk factors in these patients.

### Polycystic ovary disease (PCOD)

Another disorder associated with insulin resistance is PCOD. Women with PCOD were found to have higher AHI values than age- and BMI-matched controls and to be more likely to have OSAS (44.4 vs. 5.5%); in this study, AHI correlated with the waist-hip ratio and with the serum testosterone level in women with PCOD (103).

In another study, PCOD patients were found to be 30 times more likely to suffer from sleep-disordered breathing than controls and to be more insulin resistant (81).

In a third study, OSA was found by polysomnography in more than 50% of women with PCOD and in only 19% of controls matched for age and BMI. The OSA patients were more insulin-resistant (based on the homeostasis model assessment index) than those without OSA and were more likely to have impaired glucose tolerance than were PCOD patients without OSA (104). OSA thus seems to be highly prevalent in PCOD and to be associated with insulin resistance and impaired glucose tolerance. Nevertheless, as in type 2 diabetes, the alternative explanation for this link between PCOS and OSA may be the existence of a common determinant (*e.g.* visceral adiposity) in the two settings.

### Acromegaly and OSA

Sleep-disordered breathing (from simple snoring to severe OSA) affects most patients with acromegaly according to studies that were mostly cross-sectional (105–115). As shown in Table 1, OSA, assessed by polysomnography, was found in an average of 69% of patients with active disease in prospective or retrospective studies.

Central sleep apnea may be observed in some patients and was considered as a consequence of an increased ventilation response to carbon dioxide (116). Because OSA is more frequent than central apnea (105, 106), the associated facial skeletal, pharyngeal, and tongue modifications were initially incriminated. The main facial skeletal defect in this setting involves the mandible. Hochban *et al.* (109) found that the opening of the mandibular angle (dorso-caudal rotation) will drive to a back position of the tongue base and thereby narrow the posterior pharyngeal space at the level of the hypopharynx and the extremity of the uvula. This was not confirmed by others who concluded that, even if these anatomical disorders may predispose acromegalic patients to OSA, they are not in themselves sufficient to cause OSA, soft tissue thickening playing a major role in the onset of OSA in this setting (117). An enlarged soft palate was shown in patients with acromegaly by means of pharyngeal magnetic resonance imaging (MRI) (Fig. 2) with measurement of various cephalometric parameters (114). Generalized soft-tissue thickening is a well-known feature of acromegaly and is related to glycosaminoglycan deposition and increased collagen production by connective tissue, but also to tissue edema. We recently showed that tissue edema is due to increased renal sodium reabsorption by the distal kidney tubules, owing to direct stimulation of epithelial sodium channel by GH and IGF-I (118). The observed decrease in the signal intensity of the tongue, reflecting water/edema (108), after effective treatment of acromegaly, mirroring the changes in cardiac hypertrophy we observed by MRI (119), further supports the responsibility of pharyngeal soft-tissue edema in OSA. In fact, the potential role of fluid accumulation in OSA may not be limited to patients with acromegaly. Indeed, edematous patients have a high prevalence of OSA, and this may be related to fluid shift from the legs to the neck while the patient is recumbent, increasing pharyngeal obstruction. Such fluid shift to the neck created by applying lower body positive pressure in healthy subjects was recently shown to increase neck size and pharyngeal resistance (120, 121).

Another factor may be the overweight or obesity of some patients with acromegaly. This may explain why the reversibility of OSA after effective treatment for acromegaly is variable. Hypothyroidism (either peripheral or central) frequently associated with acromegaly may also be a contributive factor. Finally, a role of altered neuromuscular control of the pharyngeal muscles cannot currently be ruled out. Indeed, in an animal model of acromegaly (GC rats), we observed myopathy of the sternohyoid muscle, a dilator muscle of the pharynx (122).

From a clinical point of view, OSA has important consequences in the patients with acromegaly: indeed, it is

**TABLE 1.** Prevalence of OSA in patients with acromegaly (only series of more than 10 patients were considered) and effects of treatment of acromegaly

First author, year (Ref.)	n	Prevalence of OSA in active acromegaly	Type of treatment of acromegaly	Proportion of patients keeping OSA after control of acromegaly	Mean (SD) AHI before treatment of acromegaly	Mean (SD) AHI after control of acromegaly
Perks, 1980 (112) <sup>a</sup>	11	3/11 (27%) <sup>a</sup>			4.1 <sup>a</sup>	
Hart, 1985 (107)	10	4/10 (40%)			42.5 (24)	18.3 <sup>a</sup>
Pekkarinen, 1987 (111) <sup>a</sup>	11	5/11 (45%) <sup>a</sup>	S	2/3	20.6 <sup>a</sup>	
Grunstein, 1991 (106)	53	43/53 (81%)	SA	NA	39	19
Grunstein, 1994 (124) <sup>b</sup>	19	NA	S, SA, DA, RT	8/32 (25%)	NA	NA
Rosenow, 1996 (125)	54	NA				
Hochban, 1999 (109)	19	12/19 (63%)				
Weiss, 2000 (115)	55	28/34 (82%)				
Ip, 2001 (110)	14	8/14 (57%)	SA	NA	NA	NA
Herrmann, 2004 (108)	14	14/14 (100%)	SA	NA	NA	NA
Sze, 2007 (113) <sup>c</sup>	13	6/13 (46%)	S	3/6 (OSA improved in 6/6)	41 (20.5)	11.3 (13.3)
Davi, 2008 (105)	18	10/18 (56%)	S, SA, RT	6/6 (OSA improved in 5/10)	31.2 (16.4)	21.3 (18.2)
Van Haute, 2008 (114)	24	21/24 (87.5%)				
Our series <sup>d</sup>	18	12/18 (66%)	S, SA, DA GHRA	9/12 (OSA improved in 5/12)	22.5 (6.5)	19.5 (5.6)
Total		166/239 (69%)		28/67 (41%)		

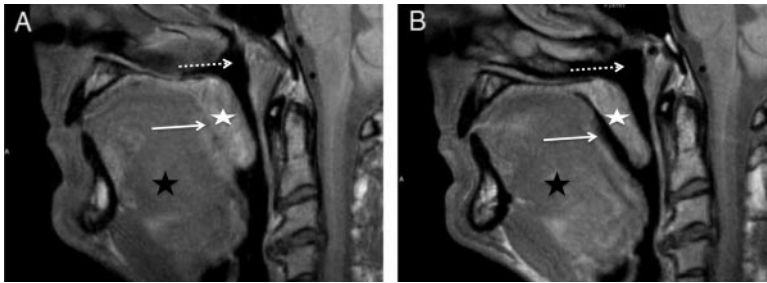
S, Surgery; SA, somatostatin analogs; RT, radiotherapy; DA, dopamine agonists; GHRA, GH-receptor antagonist; NA, not available.

<sup>a</sup> In this study, only apneas were considered for the evaluation of OSA and calculation of index (apnea index).

<sup>b</sup> Twelve of the 19 patients reported in that study were previously reported in the study by Grunstein *et al.* in 1991 (106); thus prevalence was not calculated in that study.

<sup>c</sup> In this study, prevalence refers to patients with OSA and excessive daytime sleepiness assessed by Epworth sleepiness scale score 10.

<sup>d</sup> Manuscript in preparation.



**FIG. 2.** Sagittal T1-weighted MRI sequences of the neck before (A) and after (B) effective treatment of acromegaly in a male patient with OSA. The treatment of acromegaly allowed a clear decrease in thickness of the tongue (*black star*), soft palate (*white star*), and pharyngeal walls and an opening of oropharynx space (*solid arrow*) between the tongue and soft palate and of posterior nasopharynx area (*dashed arrow*), which were associated with the cure of OSA in this patient.

likely to be the main explanation for the fatigue presented by many patients and contributes to their altered quality of life (123).

Effective treatment of acromegaly, whether surgical or medical, has been shown to improve OSA in a substantial number of patients. Results of the studies, which were more cross-sectional than prospective, are summarized in Table 1. The severity of OSA is diminished when hormonal parameters are normalized or improved (105, 107, 108, 110, 111, 113, 114, 124–126). We (127), and others (105, 108, 110, 124, 125, 128), have observed dramatic improvements in OSA after medical treatment of acromegaly with somatostatin analogs. However, in prospective studies, OSA persists in more than 40% of patients cured of acromegaly (105, 111, 113, 125). All patients should therefore be reassessed after effective treatment of acromegaly to determine whether treatment of OSA, with CPAP for example, remains necessary. The variable response of OSA to treatment of acromegaly may reflect a multifactorial pathophysiology of OSA in this setting.

## Hormone Deficiencies and OSA

### Hypothyroidism

Hypothyroidism and OSA are both frequent in the general population and show some clinical overlap.

An increased prevalence of OSA (between 25 and 35%) has been reported in patients with hypothyroidism studied prospectively or retrospectively (129–137). Central apnea may also be encountered in this setting. The main pathophysiological determinant of OSA in hypothyroidism seems to be pharynx narrowing due to soft tissue infiltration by mucopolysaccharides and protein, in the context of the generalized infiltration of skin and soft tissue, which is a well-known feature of hypothyroidism (138). However, altered regulatory control of pharyngeal dilator mus-

cles due to the neuropathy frequently observed in hypothyroidism (138) may also be involved. Depression of respiratory centers might also theoretically be involved (139), but this is unlikely given the large predominance of obstructive apnea over central apnea (131). Whether the patient is hypothyroid or not, presence of large goiters may also contribute to pharynx occlusion and OSA (140).

Replacement therapy for hypothyroidism cured OSA in most patients with OSA and hypothyroidism (131, 132, 141), possibly owing to the fact that the patients in this study were frankly hypothyroid, generally nonobese, and experienced a clear benefit (*e.g.* in macroglossia) of  $T_4$  treatment. By contrast, when patients are obese, cure rate of OSA may be less impressive (137, 142).

These findings support the recommendation that thyroid hormones and TSH be measured in all patients consulting sleep clinics for suspected or confirmed OSA, even if the prevalence of hypothyroidism is low (1–10%) in this population (132, 141, 143, 144). A combination of the two disorders will generally be coincidental, given their high prevalence in the general population. However, in the rare cases in which frank hypothyroidism is found in a patient with OSA, it seems reasonable to wait and see if a few weeks of  $T_4$  replacement can improve OSA before proposing CPAP therapy.

### Hypogonadism, androgen therapy, and OSA

A role of androgens in OSA is suggested by the male predominance of OSA (1–3). By contrast, in the general population, low testosterone levels were found to be associated with an increased risk of sleep apnea and sleep disorders in men over 65, but this was very likely related to the influence of obesity (145). In a cross-sectional study of men with sleep apnea, more severe hypoxia was associated with lower free and total testosterone levels, independently of age and obesity, and CPAP therapy increased total but not bioavailable testosterone levels (146). The mechanism for this association is poorly understood but has been postulated to be related to the effects of sleep deprivation on hypothalamic-pituitary-gonadal axis (see above).

In prospective studies, treatment with androgens in both eugonadal and hypogonadal men has been found to exacerbate or trigger the development of sleep apnea (62, 147–151). However, other authors (152, 153) found no change in OSA in older patients during testosterone therapy, and androgen blockade did not modify sleep apnea either (154). From a practical point of view, when initiating treatment with androgens, one may recommend

looking for clinical changes that may suggest occurrence of OSA and propose polysomnography in case of doubt.

### GH deficiency and replacement therapy

Several investigators have studied GH-treated patients with panhypopituitarism. A first study, in 2002, showed that GH replacement therapy influenced sleep reaction, and treatment cessation was associated with a significant decrease in slow-wave sleep and with a shift from obstructive to central apnea and hypopnea (155). In another prospective study, OSA was found to be present in 12 of 19 (63%) patients with variable degrees of pituitary deficiency acquired in adulthood and who were adequately replaced in all hormones except GH, thus suggesting a role of GH deficiency. Compared with patients without OSA, patients with OSA tended to be older men with higher BMI and waist-hip ratio values. In fact, GH treatment had various effects on OSA: two patients no longer had OSA after treatment, whereas two patients developed OSA during treatment. Overall, no change in AHI was observed during GH treatment (156). Clearly, more data are needed before drawing firm conclusions on the possible relation between OSA and GH deficiency or its treatment.

### Conclusion

Some endocrine and metabolic conditions can be associated with OSA. In rare instances, OSA may be improved or even cured by treatment of underlying endocrine disorders: this is the case of hypothyroidism and acromegaly, situations in which OSA is mainly related to UA narrowing due to reversible thickening of the pharyngeal walls.

However, when irreversible skeletal defects and/or obesity are present, OSA may persist despite treatment of endocrine disorders and may thus require complementary therapy. This is also frequently the case in patients with obesity, even after substantial weight reduction. Given the potential neurocognitive consequences and increased cardiovascular risk associated with OSA, CPAP therapy is recommended if OSA persists despite effective treatment of its potential causes.

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