Ann Natl Acad Med Sci (India), **49(3&4):** 122-131, 2013

Endocrine and Metabolic Aspects of OSA

Ravinder Goswami
Department of Endocrinology and Metabolism
All-India Institute of Medical Sciences, New Delhi

ABSTRACT

Obstructive sleep apnea (OSA) is characterized by repeated spells of apnea. Collapsibility of hypopharynx due to multiple factors involving pharyngeal dilator muscles and deposition of fat or fluid in the surrounding soft tissues are important contributing factors in its pathogenesis. OSA commonly affects obese individuals. Males are more commonly affected than the females probably due to the disturbing effect of testosterone on sleep.

The impact of OSA on human health include disturbances in endocrine and metabolic system affecting hypothalamic-pituitary-gonadal axis, adrenocorticotrophic-cortisol axis, growth hormone, antidiuretic hormones and insulin resistance. There is a tendency for predisposition of the metabolic syndrome or its components including glycemic dysregulation, hypertension, hyperlipidemia and physical parameters related to adiposity. On the other hand, several endocrine disorders such as hypothyroidism, growth hormone excess, polycystic ovarian disease and testosterone replacement are associated with increased prevalence of OSA.

There is limited information on the effect of treatment of OSA by continuous positive airway pressure (CPAP) on the endocrine and metabolic disturbances. There is a need to conduct randomized controlled trials using CPAP therapy in patients with OSA and to study its cause and effect relationship with endocrine and metabolic disturbances**.**

Correspondence : Prof. Ravinder Goswami, Department of Endocrinology and Metabolism, All-India Institute of Medical Sciences, Ansari Nagar, New Delhi – 110029. E-mail: gosravinder@hotmail.com

OVERVIEW

Deposition of fat and fluid in the soft tissues of the airways are important contributing factors in the pathogenesis of OSA (1,2). As expected, OSA is more common in obese individuals but can also be seen in non-obese subjects and children (3,4). Males are more commonly affected than the females probably due to disturbing effect of testosterone on sleep. With advancing age the protective effect of estrogen is lost leading to increased prevalence of OSA in postmenopausal women. OSA has been associated with increased incidences of diseases related to endocrine, nutritional and metabolic, nervous conditions, respiratory, skin and musculoskeletal system.

The problem of OSA and associated syndrome is also common in Indians with prevalence rate similar to that reported in the western population (5). Recently, Sharma and Ahluwalia summarized salient studies from India (5). The prevalence of OSA in North Indians and Western Indians was 9.3% and 19.5% respectively (5,6). The prevalence rates of OSA syndrome in these cohorts were 2.8% and 7.5% respectively. The trend of higher prevalence in males than females was also observed in the Indian subjects. However, these studies cannot be taken as representative of the whole Indians in view of the wide variation in the socioeconomic differences and prevalence of obesity in Indians from different geographic regions.

The purpose of the present review is to provide an overview of the endocrine manifestations covered in the Annual meeting of the National Academy of Medical Sciences held at AIIMS, Jodhpur in 2013. The endocrine implications of OSA have been covered recently in two excellent reviews by Attal and Chanson (1) and Kamenov *et al.* (2). The present review is based on relevant information on OSA summarized in these reviews and other published data. The search period was focused for studies available during 2008 to 2013. Broadly, the information can be categorized as (A) effect of OSA on endocrine disturbances (B) effect of endocrine disorders on OSA and (C) disorders where the cause and effect relationship is not clear i.e. obesity, diabetes, insulin resistance and polycystic ovarian disease (PCOD).

(A) Effect of OSA on endocrine disturbances

Effect of OSA on hypothalamic-pituitary-gonadal axis :

There is sexual dimorphism in the prevalence of OSA. This indicates the role of testosterone in sleep disturbance and protective effect of estradiol in females. Despite sexual dimorphism in the prevalence of OSA, alteration in sex hormone is a common feature in male and female patients with OSA. The low serum total testosterone level observed in OSA could be an effect of hypoxia on hypothalamic-pituitary-gonadal axis. Alternatively, it could be a confounding effect of obesity commonly associated with the OSA syndrome and related

alteration in sex hormone binding globulin (SHBG). There is insufficient data on sex hormone status (serum total and free testosterone) along with SHBG in subjects with OSA. Similarly, the effect of testosterone replacement and treatment with continuous positive airway pressure (CPAP) either alone or in combination has not been extensively studied using well-designed placebo controlled randomized control trials (RCT). Recently, Hoyos *et al.,* reported a RCT on the effect of 1000 mg of testosterone undecanoate given for 18 weeks in a group of 67 males. Testosterone supplemented group had worsening of O_2 desaturation index at 7^{th} week. The study concluded worsening of sleep disorder breathing in time dependent manner with testosterone in obese males with severe OSA (7). Meston *et al.,* reported a RCT on the effect of nasal CPAP therapy in 101 male subjects with OSA. Testosterone and SHBG showed a negative correlation with the OSA severity at baseline. Active intervention group had a significant elevation of SHBG and reversible change in serum testosterone (8).

Changes in serum prolactin levels have also been documented in patients with OSA (9). The high serum prolactin level led to a negative effect on hypothalamic-pituitary-gonadal axis in them. Recently, Macrea *et al.,* reported the effect of CPAP therapy after 11 to 39 months on serum prolactin, estradiol, FSH, LH, testosterone, glucose, cortisol and leptin (9). The CPAP therapy led to significant fall in serum prolactin levels with no change in other hormones. The higher serum prolactin values observed seems to be a consequence of OSA and not a cause of OSA as patients with prolactinoma do not have increased prevalence of OSA syndrome (10). Thus, hypothalamic-pituitary gonadal axis is impaired in patients with OSA, but the causal role of obesity, SHBG and prolactin needs further evaluation. The effect of such disturbances on quality of life, infertility and sexual dysfunction is an important area requiring further studies.

Effect of OSA on hypothalamic pituitary-adrenal and thyroid Axis:

Henley *et al.,* assessed ultradian patterns of serum ACTH and cortisol using repetitive blood sampling in 10 patients with moderate to severe OSA at baseline and at 3 months after CPAP therapy (11). The mean total ACTH and cortisol production were significantly increased at baseline and the levels of both the hormones decreased after CPAP therapy. Pre-CPAP therapy, the subjects had significantly elevated cortisol response to a single breath of 35% CO_2. Lanfranco *et al.,* observed increased ACTH response to CRH in patients with OSA, which was not explained by obesity (12). However, unlike the study by Henley *et al.,* this study could not find any significant difference in the serum cortisol and ACTH levels in obese subjects with or without OSA. The increased serum cortisol level observed in OSA has also been implicated in the pathogenesis of metabolic syndrome associated with

OSA. However, the variable data obtained for the ACTH-cortisol axis in various studies, as exemplified in the above two studies, indicates a need for further studies on this aspect. The thyroid axis has been found to be normal in most patients with OSA except for the pattern of sick euthyroid syndrome in severe OSA (2).

Effect of OSA on fluid and electrolyte disturbances :

The increased effort of breathing in OSA creates a situation of excessive negative intra-thoracic pressure. This is analogous to increased volume load to the heart resulting in increased secretion of atrial natriuretic peptide from the heart. This peptide has inhibitory effect on the arginine vasopressin and renin angiotensin aldosterone system, which can result in increased glomerular filtration. Thus, OSA favours suppression of vasopressin which could be the possible reason for the increased nocturia observed in some of the patients with OSA (2,13,14). Patients with OSA are also prone to resistant hypertension. Recently, Pimenta *et al.,* evaluated 97 patients with resistant hypertension by overnight polysomnography and assessed 24-h urinary sodium and aldosterone excretion (15). 28.9% of the patients had hyperaldosteronism and 77.3% had OSA. Urinary sodium level was found to be an independent predictor of severity of OSA only in patients with hyperaldosteronism. The authors suggested restriction of dietary salt as a treatment strategy for management of OSA in resistant hypertension.

(B) Effect of endocrine disorders on OSA

Growth hormone excess and OSA :

Acromegaly is associated with a remarkably high prevalence of OSA. Recently Roemmler *et al.,* assessed the prevalence of sleep apnea by polysomnography in 52 patients with acromegaly (16). Twenty three of them had controlled disease activity with GH levels <1 μg/l and normal IGF-1 levels and 12 had active acromegaly despite use of somatostatin analogues. The prevalence of OSA was 66% in patients with active disease and 48% in the cured group. Patients with acromegaly and OSA had higher mean HbA1c and higher prevalence of hypertension than those without OSA. Though the OSA correlated with BMI, age and disease activity, it showed no significant correlation with duration of the disease and serum growth hormone. Interestingly, five subjects had evidence of central sleep apnea either in isolated form or mixed with OSA. Thus, patients with and without active acromegaly are prone to OSA as well as central sleep apnea. The facial skeletal defects associated with acromegaly such as prognathism, widened angle of the jaw due to mandible position, thickened soft tissues of the nasopharynx including soft palate and uvula, with fluid retention due to salt retaining effect of growth hormone are major factors responsible for increased prevalence of OSAS in the acromegaly. Besides, excess body weight and central hypothyroidism associated with pituitary mass lesion, hyperprolactinemia leading

to hypogonadism and changes in the neuromuscular structure of the pharyngeal muscle also possibly contribute in increased prevalence of OSA in acromegaly. Irreversibility of several of these changes especially skeletal structure might explain the persistence of the OSA syndrome after successful medical or surgical therapy (2).

Paradoxically, adult patients with isolated growth hormone deficiency as exemplified by patients with panhypopituitarism who were adequately replaced with all hormones except growth hormone also demonstrate increased prevalence of OSA. Replacement with growth hormone resulted in improvement in OSA in some of these patients but also had a worsening effect in others (2, 17).

Hypothyroidism and OSA :

Increased sleepiness and weight gain are features common to both OSA and hypothyroidism. The prevalence of OSA has been found to be 25-35% in patients with hypothyroidism (2,18). Kapoor *et al.,* studied 336 consecutive adult patients undergoing polysomnography for suspected OSA and similar age and sex matched controls (18). The prevalence of hypothyroidism was only 1.4% in OSA. Moreover, all the subjects had only subclinical hypothyroidism indicating lack of case for routine screening for hypothyroidism in patients with OSA. Narrowing of the pharynx due to infiltration of the soft tissue by mucopolysaccharides might alter the control of the respiration (2). Presence of large goitre and macroglossia are the possible contributory factors for the pathogenesis of OSA in hypothyroidism (19). Medical replacement therapy with L-thyroxin or surgery can reverse features of OSA syndrome specially when there is no obesity. Reiher *et al* has recently shown the important role of goitre in the pathogenesis of OSA (19) 71% of patients had Berlin questionnaire suggestive of OSA before thyroidectomy, which was decreased to 51% after surgery.

Obesity, metabolic syndrome and OSA:

Prevalence of obesity is high in patients with OSA. Peppard *et al.,* showed that a 10% weight gain would result in 32% increase in AHI (20). Similar relationship between obesity and OSA is observed in childhood obesity also (21). Moraleda-Cibrián and O'Brien investigated the association between short sleep duration, obesity and OSA in 306 children undergoing polysomnography and observed prevalence of obesity, short sleep duration and OSA as high as 32 %, 39.5 % and 78 % respectively (21). Children with OSA had a similar frequency of short sleep duration than those with no OSA. However, in children with short sleep duration, the odds ratio for obesity was 2.5 (95 % CI 1.3-4.9) compared to children with normal sleep duration even after accounting for the presence of OSA. The authors concluded that reduction in total sleep duration by 1 h was associated with a higher risk for obesity in children. Various aspects of obesity which could determine the

presence of OSA include (a) degree of fat deposition around upper airways and lateral wall of nasopharynx as reflected by neck circumference (b) reduced pulmonary volume consequent to abdominal obesity and increased respiratory effort leading to decrease pulmonary traction of the upper airways and (c) impairment of the dilator muscle (2). Use of different criteria to define obesity such as BMI, waist or neck circumference and visceral fat in various studies could explain the variable prevalence of metabolic syndrome in OSA (2,3). Reduction of obesity by bariatric surgery can reverse or improve OSA (22). Greenberg *et al.,* reported up to 75% reduction in prevalence of OSA after bariatric surgery. However, there is a tendency of relapse for OSA after surgery. This could be related to that fact that despite successful surgery, some of the patients continue to have significant fat deposition in the neck tissues (2, 22).

Patient with OSA have high prevalence of metabolic syndrome with incidence as high as 60% (2,3). The prevalence of various components of metabolic syndrome such as dyslipidemia (hyper cholesterolemia in males and decreased HDL/increased triglycerides in females) waist to hip ratio, hypertension, insulin resistance and impaired fasting glucose have been found to be high in OSA. However, the independent link of metabolic syndrome with OSA after adjusting for obesity is not clear. Kamenov *et al.,* reviewed various studies on the prevalence of metabolic syndrome in patient with OSA (2). Several observational studies indicated association of OSA with metabolic syndrome or its individual components. Coughlin *et al.,* carried out an RCT on the effect of CPAP on metabolic syndrome in 34 subjects with OSA (23). Though arterial pressure decreased after 6 weeks of CPAP, there was no change in the insulin resistance or lipid profile (23). Hoyos *et al.,* recently studied 65 CPAP naïve adult men without diabetes who had moderate to severe OSA (24). Subjects were randomized to receive either real or sham CPAP for 12 weeks. Though the AHI was lower on CPAP after 12 weeks, there were no between-group differences after 12 weeks in the visceral fat, insulin sensitivity index and liver fat. The authors concluded that CPAP therapy in men with OSA would not lead to significant reduction of visceral adiposity (24).

The pathogenesis of metabolic syndrome in OSA is not clear but could be related to pro-inflammatory cytokines and hormones produced from visceral fats including leptin, omentin, IL-6 and TNF-alpha. Kurt *et al*., studied 46 patients with newly diagnosed OSA patients and 35 normal subjects (25) and observed elevated circulating omentin in OSA. Both obesity and OSA can independently result in hyperleptinemia. Successful treatment of OSA by CPAP is predicted to decrease hyperleptinemia. Recently, Zirlik *et al.,* studied 10 patients with newly diagnosed OSAS and healthy volunteers. Patients had significantly higher plasma omentin-1 than healthy volunteers which decreased towards the values observed in the controls after three

months of CPAP therapy (26).

The plasma melatonin peaked at 2.00 a.m. in the healthy volunteers but at 6.00 a.m. in patients with OSA. The abnormality in melatonin returned to normal after CPAP therapy. Whether these abnormalities associate with OSA independent of insulin resistance is not clear. Thus, there is a need to generate further data based on placebo controlled randomized trial with CPAP.

Diabetes and OSA :

Cross sectional and experimental studies suggest a link between OSA and increased prevalence of diabetes. However, the issue related to false association between OSA and DM exists in view of co-linear association between obesity and DM. Moreover, the methods used to rule out diabetes or to adjust obesity vary in different studies (2,3). These factors therefore do not allow firm association of diabetes with OSA. Tassone *et al.,* studied insulin dynamics and glucose metabolism in 30 obese patients with OSAS and matched controls (27). The composite insulin sensitivity index values were significantly lower in OSAS than in the obese and normal subjects. The authors concluded that obese patients with OSA syndrome had higher insulin resistance than patients with simple obesity, independent of the degree and distribution of adiposity. Recently, Bozkurt *et al.,* assessed 190 non-diabetic subjects grouped as controls, mild OSA, moderate OSA and severe OSA after polysomongraphy (28). Subjects with more severe OSA tended to have lower vitamin D levels which also correlated with increased prevalence of insulin resistance, pre-diabetes and diabetes status (28). Thus, vitamin D deficiency might also play a role in the OSA associated glycemic dysregulation.

West *et al.,* carried out a RCT in patients with OSA and DM and observed no significant effect on the HbA1c values (29). The pathogenesis of diabetes in OSA is similar to that of Type 2 DM with predominant effect on insulin sensitivity. Though data on insulin sensitivity in human is limited, there is strong support from animal studies on the pathogenetic mechanism of diabetes in OSA (30,31). Restriction of sleep in animal resulted in increased prevalence of glucose intolerance, hypertension and impaired pancreatic beta cell regenerative capacity especially in animal with hyperglycemia. Yokoe *et al.,* developed a chronically catheterized, unhandled, lean adult male C57BL/J model to examine the effects of intermittent hypoxic exposure and exogenous glucose infusion on the diurnal pattern of blood glucose, and pancreatic beta-cell growth and function (31). Intermittent hypoxia impaired glucose homeostasis only during periods of hypoxic exposure. Presence of hyperglycemia increased the hypoxic susceptibility of beta-cells. The pathogenesis of increased prevalence of diabetes in OSA in human could also be related to increased serum cortisol, oxidative stress and its effect on lipid peroxidation, up-regulation of nuclear factor-kB (2,3).

Polycystic ovarian syndrome and OSA:

There has been increasing awareness about the association of PCOD with OSA (2,32,33). The prevalence of OSAS is increased by 10 fold in these patients (2). Vgontzas *et al.,* observed 30 times higher risk of OSA among patients with PCOD compared to age matched controls (33) which was also associated with higher degree of insulin resistance, waist hip-ratio and glucose intolerance. The increased association between the two disorders is not clear but could represent a common pathogenesis such as insulin resistance or could be due to increase in serum testosterone in patients with PCOD and its destabilizing effect on sleep.

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