Obstructive sleep apnoea syndrome related morbidities and their treatment: A matter of mandate

*Kuldeep Patial 1, Vishwajeet Rohil 2, Sunil Kumar Ratra, Bharti Patial, Rajendra Kumar Behera 1

1School of Life Sciences, Sambalpur University, Odisha
2Dept. of Biochemistry, Vallabhbhai Patel Chest Institute, University of Delhi

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ABSTRACT

Obstructive sleep apnoea syndrome is the most prevalent form of sleep disorder breathing characterized by persistent pauses of breathing during sleep time. The disorder is manifested by upper airway obstruction and excessive day time somnolence (EDS) which directly affect the quality of life of the patients. Reports from previous studies revealed that occurrence rate of obstructive sleep apnoea syndrome is approx 13.7% among habitual snorers and 3.6% among non-habitual snorers which is equivalent to other major diseases and contributes to morbidity and mortality in developed as well as in developing countries, like India. The disorder is in association with metabolic syndrome and many serious cardiovascular conditions are stimuli of various inflammatory pathways in disease progression. The primary pathophysiologic abnormality in sleep disorder breathing is insulin resistance. Recurrent hypoxic function contributes to delay in hepatic function. The occurrence of oxidative stress with sleep disorder breathing also emerged as a public health issue. It has been reported that, severe obstructive sleep disorder patients have higher levels of plasma leptin than patients with mild and there occurs a positive correlation which is independent of age and BMI, between the plasma leptin levels and the severity of disease. Consequently hyperleptinemia may be considered a predictive marker of obstructive sleep disorder. The first line treatment of diagnosed obstructive sleep disorder syndrome includes nasal continuous positive airway pressure. Apart other treatments include surgical procedures, mandibular advancement splint and drugs which treat daytime somnolence. Recent study shows that oral intake of antioxidants not only reduces oxidative stress but also improves sleep disorder breathing and excessive day time somnolence. In this review, an exhaustive scan is done from past till up to date which are in concern of the morbidities along with their therapeutic measures associated with obstructive sleep disorder syndrome.

Key words: obstructive sleep disorder syndrome; excessive day time somnolence; sleep disorder breathing; body mass index.

INTRODUCTION

Decades ago, snoring was considered a sign of a sound sleep. But things started changing in 1966, when obstructive sleep apnoea (OSA) was first identified as a disorder.1 Obstructive sleep apnoea syndrome is the most prevalent form of sleep disorder breathing characterized by persistent pauses of breathing during sleep time. The disorder is manifested by upper airway obstruction and excessive day time somnolence (EDS).2 The very first symptom of obstructive sleep apnoea syndrome is EDS, which directly effects the quality of life of the patient. The minimum duration of an apneic episode is 10 seconds and it occurs with reduction in oxygen saturation of blood and neurological EEG arousal.3 When obstructive sleep apnea is accompanied by excessive daytime somnolence, it is known as obstructive sleep apnea syndrome (OSAS).

The studies conducted in the past reveal a continuous increase in number of patients being referred for OSAS. Reports from previous studies in north India revealed that occurrence rate of obstructive sleep apnoea syndrome is approx 13.7% (occurrence in males was 4.9% and in females was 2.1%)4 among non-habitual snorers and 13.7% among habitual snorers which is equivalent to other major diseases like diabetes mellitus and asthma5 and contributes to morbidity and mortality in developed as well as in developing countries also, like India.4,7 The incidence rates among males and post-menopausal females are

*Corresponding Author Address: *Kuldeep Patial, School of Life Sciences, Sambalpur University, Odisha, India,
E-mail: kuldeepdr@hotmail.com
similar thus, this disorder is very often an under diagnosed entity. The first line treatment of diagnosed OSAS includes nasal continuous positive airway pressure. Untreated OSAS patients were dangerous road drivers shows excessive day time sleepiness, psychomotor deficits, low work productivity and absenteeism. The disorder is in association with many serious cardiovascular conditions like myocardial infarction, pulmonary hypertension, systemic hypertension and ventricular arrhythmias are stimuli of various inflammatory pathways in disease progression. There is nocturnal polyuria and natriuresis and urge to urinate is also high among these patients and leads to frequent EEG arousal.

**Functions:** Multiple theories have emerged to explain the function of sleep. The functions of sleep are includes:

**Restoration:** Wound healing has been shown to be affected by sleep. Gumustekin et al., shows sleep deprivation hindering the healing of burns in rats. Immune system and metabolism is affected by sleep deprivation. Zager et al., reported that ten ninety day old rats which were deprived of sleep for 24 hours when compared with a control group shows a 20% decrease in white blood cell count, which is a significant change in the immune system.

The parameter of somatic growth affected by sleep duration is yet to be explored. Experiment by Jenni et al., recorded growth, height and weight, as correlated to parent-reported time-in-bed in 305 children over a period of nine years (age 1-10). It was found that "the variation of sleep duration among children does not seem to have an effect on growth".

It has been shown that sleep, slow-wave sleep (SWS), does affect growth hormone levels in adult men. One hundred and forty-nine healthy men ages 16-83 were studied by Van Cauter et al., in 2000. During eight hours sleep, it was found that subjects with a high percentage of SWS (average 24%) also had high growth hormone secretion, while subjects with a low percentage of SWS (average 9%) had low growth hormone secretion.

**Ontogenesis:** Previous studies reveal that REM sleep, the activity occurring during neonatal REM sleep (or active sleep) seems to be particularly important to the developing organism. Studies investigating the effects of deprivation of active sleep have shown that deprivation early in life can result in behavioral problems, permanent sleep disruption and decreased brain mass.

**Memory processing:** The phenomenon of sleep is widely arrayed by memory. Turner et al., reported that sleep deprivation affect the working memory which keeps information active for further processing and supports higher-level cognitive functions including ascertaining to decision making, reasoning, and episodic memory.

**Effect of food and drink on sleep**

**Drowsiness**
- Tryptophan
  Food containing amino acid tryptophan causes sleepiness. Carbohydrates make tryptophan more available to the brain and carbohydrate laced heavy meals cause drowsiness when accompanied with tryptophan.
- Melatonin
  Melatonin is a naturally occurring hormone that regulates sleepiness. It is made in the brain by converting tryptophan into serotonin and then into melatonin, which is released at night by the pineal gland in the brain to induce and maintain sleep. Melatonin is widely used in sleep aids.
  - The "Post-Lunch Dip"
    Some people have a temporary drop in alertness in mid-afternoon. This is most commonly known as the post-lunch dip. A large meal can make a person feel sleepy, especially if it is rich in carbohydrates, but the post-lunch dip is mostly an effect of our biological clocks. People naturally feel tired at two different times of the day: about 2:00 AM and 2:00 PM. It is this natural drop in alertness coupled with carbohydrate and protein consumption from afternoon meals that creates the "Post-Lunch Dip".
    - Alcohol
      Alcohol is commonly used as a sleep aid, however, it is not a good aid for sleep because although it helps one relax and fall asleep in the short term, it often disrupts sleep throughout the night and can keep one from entering the deeper stages of sleep, which can cause one to wake up tired regardless of having spent a proper amount of time asleep.

**Stimulation**
- Caffeine
  Caffeine is a stimulant that slowing the action of the hormones in the brain that make us feel sleepy. A strong dose of caffeine can stimulate the mind for a short time, but can cause a crash in alertness as it wears off.

**Sleep disorders associated with mental, neurologic or other medical disorders**

**A. Association with mental disorders**
1. Psychoses
2. Mood disorders
3. Anxiety disorders
4. Panic disorders
5. Alcoholism
B. Associated with neurologic disorders
Cerebral degenerative disorders, Dementia, Parkinsonism, Fatal familial insomnia, Sleep-related epilepsy. Electrical status epilepticus of sleep, Sleep-related headaches.

C. Association with other medical disorders
Sleeping sickness, Nocturnal cardiac ischemia, chronic obstructive pulmonary disease, Sleep-related asthma. Sleep-related gastroesophageal reflux, Peptic ulcer disease, Fibromyalgia. A sleep diary is used as a tool to diagnose, measure improvements in sleep disorders. The Epworth sleepiness scale is another diagnostic tool to assess day time sleepiness.

D. Obstructive sleep apnoea
Obstructive sleep apnoea is a commonest type of sleep apnoea caused by obstruction of the airway which is characterized by recurrent pauses in breathing during sleep. These episodes, called apnoeas (“without breath”). In obstructive sleep apnea, breathing is interrupted by a physical block to airflow, despite the effort to breath. 29 These events occur simultaneously and the patient oscillates between wakefulness and sleep. In severe cases, these events can occur more than 100 times per hour and the duration of each event lasts for 20–40 seconds or more.

The individual with sleep apnoea hardly aware of having breathing difficulty, even after awakening. Sleep apnoea is recognized by others witnessing the individual during episodes or is suspected because of its bad effects on the body. Symptoms may be present for years, even decades without identification.

Risk factors: High risk of obstructive sleep apnoea among individuals with decreased muscle tone, increased soft tissue around the airway, and structural features that give rise to a narrowed airway. 30 Sleep apnoea occur more in men with increased body mass in the torso and neck, especially through middle age and older. The physiological difference leads to higher predominance in males when compared with females due to accentuated levels of progesteron. Prevalence in post-menopausal women approaches that of men in the same age range. 31

Unusual facial features that occur in recognizable syndromes. Some of these craniofacial syndromes are genetic, others are from unknown causes. In many craniofacial syndromes, the features involve are nose, mouth and jaw, or resting muscle tone, and put the individual at risk for obstructive sleep apnea syndrome. 32 Down syndrome is one syndrome. In this chromosomal abnormality, presence of obstructive sleep apnoea more likely. The specific features in Down syndrome that influence to obstructive sleep apnoea include: relatively low muscle tone, narrow nasopharynx, and large tongue. 33 Obesity and enlarged tonsils and adenoids. 34 conditions that occur commonly in the western population, are much more likely to be obstructive in a person with these features than without them. Obstructive sleep apnoea does occur even more frequently in people with Downs syndrome than in the general population. 33

In craniofacial syndromes, the abnormal feature may actually improve the airway, but its correction may put the person at risk for obstructive sleep apnoea after surgery, when it is modified. Cleft palate syndromes are such an example. During the newborn period, all humans are obligate nasal breathers. The palate is both the roof of the mouth and the floor of the nose. Having an open palate may make feeding difficult, but generally does not interfere with breathing, in fact - if the nose is much obstructed an open palate may relieve breathing. There are a number of clefting syndromes in which the open palate is not the only abnormal feature; additionally there is a narrow nasal passage - which may not be obvious. In such individuals, closure of the cleft palate- whether by surgery or by a temporary oral appliance, can cause the onset of obstruction. 32

Skeletal advancement in an effort to physically increase the pharyngeal airspace is often an option for craniofacial patients with upper airway obstruction and small lower jaws (mandibles). These syndromes include Treacher collins syndrome and Pierre Robin Sequence. 32 Mandibular advancement surgery is often just one of the modifications needed to improve the airway, others may include reduction of the tongue, tonsillectomy or modified uvulopalatoplasty.

Signs and symptoms
The most common sign and symptoms of sleep apnoea are daytime somnolence, restless sleep and heavy snoring (with periods of silence followed by gasps). The less common symptoms includes morning headaches, lack of concentration, mood swings such as irritability raised, anxiety and depression, lack of memory, increased heart rate and blood pressure, decreased sex drive, unexplained weight gain, increased urination and/or nocturia, frequent heartbeat or gastroesophageal reflux disease and night sweats while sleeping. In adults, the most typical individual with obstructive sleep apnoea syndrome suffers from obesity, with particular heaviness at the face and around the neck. Obesity is not always present with OSA, in fact a significant number of adults with normal body mass indices (BMI) have decrease in muscle tone causing airway collapse.
and sleep apnoea. The exact cause of decrease in tone is not found yet. The characteristic symptoms of obstructive sleep apnoea in adults is excessive daytime somnolence. Typically, an adult with severe obstructive sleep apnoea may fall asleep for short periods if given any opportunity to sit or rest. This event sometimes occurs during conversations with others at social gatherings.

**IMPACT OF OBSTRUCTIVE SLEEP APNOEA ON POPULATION**

Without treatment, the sleep deprivation and lack of oxygen due to sleep apnoea increases health risks such as cardiovascular disease, high blood pressure, stroke, diabetes, clinical depression, weight gain and obesity. The most serious result of untreated obstructive sleep apnoea is to the heart. In severe cases, there are increases in pulmonary pressures that are transmitted to the right side of the heart. This can result in a severe form of congestive heart failure (cor pulmonale).35, 36, 37 Obstructive sleep apnoea syndrome elevates arterial pressure.37 When high blood pressure is caused by OSA, it is distinctive in that, unlike most cases of high blood pressure, the readings do not drop significantly when the individual is sleeping. Stroke is associated with obstructive sleep apnoea.36 Sleep apnoea sufferers also have a 30% higher risk of heart attack or death than those unaffected.36

**ASSOCIATION OF OBSTRUCTIVE SLEEP APNOEA WITH DIFFERENT DISEASES**

Sleep apnoea often leads to excessive daytime sleepiness and sleep deprivation. The adverse conditions associated with sleep apnea are numerous. To name a few, there is impaired cognitive and neuropsychological functioning, reduced quality of life, occupational and motor vehicle accidents, hypertension, brady- and tachyarrhythmia, coronary artery disease, myocardial ischemia, cerebrovascular accidents, cardiomyopathy/congestive heart failure, pulmonary hypertension, insulin resistance and increased overall mortality.39

**Sleep apnoea and metabolic syndrome (MS):**

OSAS has an association with the MS. A number of aspects on OSAS it is suggested that sleep apnoea is a sign of the metabolic syndrome. Indeed, there is a strong relationship of OSAS with obesity, male gender (android-central obesity), post-menopausal increase of its occurrence, systemic effects, e.g. hypertension and diabetes, and the natural course of symptoms, all overlapping with the factors associated with MS.46-48 It appears that in both conditions there is a vicious cycle of weight gain (particularly from young adulthood to middle age), snoring, development of pauses breath, daytime somnolence, further weight gain, deterioration of breathing abnormalities, and more severe daytime somnolence, all pointing towards a systemic illness rather than a specific abnormality.

**Sleep apnoea and hypertension:** Systemic hypertension is observed in 50-70% of patients with OSAS. Numerous large cross-sectional studies have provided evidence that OSAS is a significant risk of disease for developing hypertension, not depending on obesity, age, alcohol drinking, and smoking.49-50 Even though some studies have shown slight reductions in diastolic blood pressure after treatment of the OSAS with nasal CPAP,51-53 no study has shown that long term use of nasal CPAP treatment lowers the blood pressure.

**Sleep apnoea and Insulin resistance:** Occurrence of MS is high in Asian Indians.54-56 It has been hypothesized that excess body fat and low muscle mass may explain the hyperinsulinemia and high risk of type 2 diabetes in Asian Indians. Several studies have reported an association between OSA and insulin resistance. It is interesting to note that Ip and associates37 observed such an association even in non-obese subjects. This statement indicates that OSA may have a bearing in development of diabetes mellitus in subjects with lean and normal body weights, which is commonly observed in India.26 Punjabi et al., reported insulin resistance even in mild forms of sleep apnoea.58 Thus taken together, these studies provide compelling evidence in favor of an independent association between OSAS and insulin resistance independent of obesity.

**Sleep breathing disorder, Cytokines, Insulin resistance and excessive daytime somnolence:**

Excessive daytime somnolence (EDS) is a major symptom of obstructive sleep apnoea syndrome. Tumour necrosis factor- alpha (TNF-α), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) are involved in physiological sleep regulation. Their increased discharge to humans is associated with somnolence and tiredness.59 Vgontzas *et al.*, reported that TNF-α and IL-6 was significantly elevated in sleep apneics.60 TNF-α was elevated in narcoleptics also. Both these cytokines were positively correlated with the presence of EDS. Sleep breathing disorder is very common disorders in which insulin resistance is a primary pathophysiological abnormality (eg. Polycystic ovarian syndrome).61 It is reported that Indians have a higher C-reactive protein (CRP) than do European whites.62, 63 It is also likely that Indians have higher levels of TNF- α and IL-6.64, 65 Elevated plasma TNF-alpha levels have been associated not only with obesity and insulin resistance but also with hypertriglycerideremia and
glucose intolerance, and negatively correlated with HDL cholesterol. Therefore a close relation exists between TNF-alpha, CRP, IL-6 and metabolic syndrome.

Sleep apnoea and hyperleptinemia and hypoleptinemia: Leptin is an adipocyte-derived hormone that controls body weight through control of appetite and use energy. Leptin levels is associate with BMI and insulin levels, and its secretion is further modified by the stress system and cytokines. Several studies have shown that there is a association between sleep apnoea and hyperleptinemia that correlates to insulin levels. Vgontzas et al., showed that apnoea/hypopnea index did not make an additional contribution to leptin levels, and suggested that the increase in leptin levels in sleep breathing disorder may be related to the higher amount of visceral fat and/or cytokines.

One study suggest that, individuals with severe OSA have higher levels of plasma leptin than individuals with mild OSA and there is a positive correlation, independent of age and BMI, between the plasma leptin levels and the severity of disease in OSA. These results suggest that hyperleptinemia may be a predictive marker of OSA.

Another study suggests that, individuals with obstructive sleep apnoea (OSA) are frequently obese and are predisposed to weight gain. They also have heightened sympathetic drive, are associated with low levels of plasma leptin. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index.

Sleep apnoea and obesity: Obesity has a major part to play in sleep apnoea. Studies have shown that visceral fat accumulation is an important risk factor for Obstructive Sleep Apnoea in obese subjects and the AHI is significantly related with intra-abdominal fat but not with subcutaneous fat in the neck region or parapharyngeal fat. Also visceral fat, which is closely associated with insulin resistance, linked more strongly to sleep breathing disorder than subcutaneous or total fat. On the basis of above findings it is clear that visceral obesity which is determined by both genetic and environmental factors gradually cause worsening of metabolic syndrome symptoms and sleep apnoea. Sleep apnoea in turn may deteriorate visceral obesity and MS by providing a stress stimulus and causing nocturnal elevations of hormones that raise visceral adiposity, metabolic abnormalities, and cardiovascular complications (Fig.1).

Metabolic abnormalities and upper airway during sleep: Sleep apnoea is a disorder that is identified by frequent collapse of the upper airway during sleep caused periods of intermittent hypoxia and sleep fragmentation. However, some data give hints for the linkage between metabolic abnormalities related with sleep apnoea and upper airway collapse. First, it has been observed that in humans and animals, insulin dependent diabetes mellitus can cause an overall depression in ventilatory control mechanisms, whereas both leptin deficiency and leptin resistance may cause

Fig. 1. A heuristic model of the complex feed forward associations between visceral fat/insulin resistance, inflammatory cytokines, stress hormones, excessive daytime somnolence and tiredness, and sleep apnoea.
respiratory depression in obese individuals, especially during sleep.82 Secondly, the reported inflammation of upper airway tissues may be associated primarily to obesity, a condition of systemic inflammation. Thirdly, obesity/insulin resistance, by releasing growth factors, may cause soft tissue edema in the neck. Finally, male type of obesity (central) may affect severely on upper airway function than female type of obesity (peripheral).83 Thus, the observed hypercytokinemia, hyperleptinemia, and hyperinsulinemia/visceral adiposity, through central and peripheral effects, may cause a collapse of the upper airway during sleep. It should be kept in mind that the number of apneas only somewhat explains the symptoms related with sleep apnoea, such as somnolence and cardiovascular problems, the metabolic abnormalities present in symptomatic sleep apnea may cause these symptoms through pathways independent of the airway collapse.

Sleep apnoea and hepatic function: There is a relation in between obstructive sleep apnoea syndrome and non-alcoholic steatohepatitis (NASH) in obese individuals and may cause to development of non-alcoholic fatty liver disease from steatosis to NASH.84 In obstructive sleep apnoea syndrome, there occurs chronic intermittent hypoxia (CIH) during sleep, CIH leads to lipid peroxidation and inflammation in the livers of mice on a high-fat, high-cholesterol diet.85 Numerous studies suggest that liver injury might be due to obstructive sleep apnoea syndrome independent of overweight and other parameters of MS.86-88 Thus hypoxia in obstructive sleep apnoea syndrome plays a role in pathogenesis of NASH. Hepatic steatosis is also linked with insulin resistance in humans89, 90 and in various animal models,91,92 increases the possibility that enhancing insulin sensitivity may reduce hepatic fat deposition. It is seen that hepatocytes from fatty livers have increased sensitivity to anoxia84 and recurrent hypoxic episodes in patients with obstructive sleep apnoea syndrome could delay hepatic function. Most patients with NASH have insulin resistance and there is a near common association between NASH and insulin resistance irrespective of obesity. Insulin resistance is present in mild as well as advanced cases of NASH.89 Further studies are needed to assess whether treatment of obstructive sleep apnoea syndrome may improve liver function.

Sleep apnoea and oxidative stress: Oxidative stress is caused by an imbalance between the production of reactive oxygen species and the biological system’s ability to readily detoxify the reactive intermediates or easily repair the resulting damage. Oxidative stress is a large increase (becoming less negative) in the cellular reduction potential, or a large decrease in the reducing capacity of the cellular redox couples, such as glutathione.96,97 The main source of reactive oxygen under normal conditions in aerobic organisms is maybe the leakage of activated oxygen from mitochondria during normal oxidative respiration. Other enzymes capable of producing superoxide are xanthine oxidase, NADPH oxidases and cytochromes P450. The best studied cellular antioxidants are the enzymes superoxide dismutase (SOD), catalase, and glutathione peroxidase.

OSA is identified by frequent night time breath obstruction of the upper airway. Each episode of airway obstruction is generally followed by a significant decrease of arterial oxygen saturation, which rapidly normalizes after breath resumes. These repeated changes of oxygen saturation could be measured equivalent to recurrent episodes of ischemia-reperfusion injury, which causes damage after the restoration of blood flow to ischemic or hypoxic tissues. Although several mechanisms are involved, such damage is mainly attributed to the production of reactive oxygen species (ROS) during reoxygenation.98,99 ROS are highly reactive molecules that interact with nucleic acids, lipids, and proteins, and are considered to have an important role in the development of cardiovascular disease. In patients with untreated OSA, episodes of hypoxiareoxygenation occur frequently during each hour of sleep and may happen every night for several decades, so this cumulative oxidative stress may play a role in the onset of cardiovascular complications. Studies have provided evidence that supports an increase of oxidative stress in OSA. Schulz et al., (2000)100 and Dyugovskaya et al.,101 detected an increase in the production of ROS in OSA, while Barcelo et al.,102 demonstrated an increase of plasma lipid peroxides. Christou et al.,103 and Singh et al.,104 proved that patients with severe OSA have a reduced antioxidant capacity. In addition, Carpagnano et al.,105 found an increase of the 8-isoprostane level in the exhaled breath condensate in OSA patients. All of these studies have showed a significant relationship between OSA and oxidative stress. It is well known that the occurrence of asymptomatic sleep breathing disorder is several times higher than that of recognized sleep breathing disorder.106 Thus, oxidative stress in persons with sleep breathing disorder may also be a public health issue.

Possible treatments of obstructive sleep apnoea
There are a variety of treatments for obstructive sleep apnoea, depending on an individual’s medical history, the severity of the disorder and, most importantly, the specific cause of the obstruction.
1. Obstructive sleep apnoea in children is usually due to chronically enlarged tonsils and adenoids. Tonsillec- tomy and adenoectomy are curative.

2. The treatment for obstructive sleep apnea in adults:
   a) Some treatments include lifestyle changes.
   b) Weight loss and quitting smoking. Some people are helped by special pillows or devices that keep them from sleeping on their backs or oral appliances to keep the airway open during sleep. If these traditional methods are not adequate, doctors usually recommend continuous positive airway pressure (CPAP).
   c) Surgical procedures that can be used to remove and tighten tissue and widen the airway, but the success rate is not high.
   d) The most broadly used current therapeutic intervention is positive airway pressure, (CPAP) continuous positive airway pressure with constant pressure which is the most common treatment for obstructive sleep apnoea.
   e) (VPAP) Variable positive airway pressure also known as bilevel or BiPAP, provides two different pressures and is sometimes used with patients who have other coexisting respiratory problems.
   f) (APAP) Automatic positive airway pressure adjusts pressure continuously, increasing it when the user is attempting to breathe.

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Kuldeep Patial et al., World J Pharm Sci 2015; 3(5): 971-980
