REVIEW ARTICLE

Obstructive Sleep Apnea & Diabetes Mellitus

Qureshi Waseem, G. Hassan*

Introduction

Obstructive Sleep Apnea (OSA) is the most common form of sleep-disordered breathing (SDB) worldwide, being more common among middle-aged adults and has been reported to affect 24% of men and 9% of women (1-3). The episodes of snoring may be witnessed by a family member or bed partener, although, the patients with OSA may not be aware that they are apneic or may not remember to resume breathing. Apneas are defined as breathing pauses 10 seconds and hypopneas as 10 second events where there is continued breathing but the ventilation is reduced by at least 50% from the baseline. Several such episodes of apnea/hypopnea may occur throughout night leading to fragmented sleep and further consequences. The severity of OSA is determined by Apnea-Hypopnea index (AHI), which represents number of apneas plus hypopneas per hour of sleep. Normally, it is <5, and the value more than this is suggestive of OSA (4-5).

Recent evidences favour the fact that severe OSA is independently associated with diabetes mellitus (DM) in patients who report excessive sleepiness during daytime (6,7).Diabetes Mellitus carries major morbidity and is a leading cause of death, attributed to its devastating complications. Type 2 DM affected an estimated 5% of the world's population in 2003, and in the USA, its prevalence is projected to rise from 14.2% in 2003 to 26.2% in 2025 (2). As per the recent predictions, over 360 million people will have diabetes by the year 2030. The prevalence of type 2 DM is rising much more rapidly because of increasing obesity and reduced activity levels as countries become more industrialized (8). On the other side, recent literature demonstrated that 23 % of the people with type 2 DM had OSA (9); the later is independly associated with DM (6,10) and can increase in a similar way as DM, in future. This information prompted us to review this subjects with available scientific background in order to make medical community aware of this disorder.

Normal Sleep and Glucose Homeostasis

Human Sleep is generally consolidated into a 7 to 9 hour period, leading to an extended period of fasting overnight. Both pancreatic beta-cell responsiveness and insulin sensitivity are influenced by sleep. Despite the extended fast during overnight sleep, blood glucose levels remain stable or fall only minimally. In contrast to this, when individuals are awake and fasting in a recumbent position without any physical activity, glucose levels decrease by 10 to 20mg/dL over a 12- hour period (11). Sleep and the circardian rhythm play roles in modulating insulin production, insulin sensitivity, glucose use, and thus glucose tolerance throughout night. In the normal healthy individuals, glucose tolerance varies throughout the day, plasma glucose responses to exogenous glucose are markedly higher in the evening than in morning, and glucose tolerance is at its minimum in the middle of might. The reduced glucose tolerance during the evening and sleep is partly caused by a reduction in insulin sensitivity concomitant with a reduction in the insulin secretary response, a marked decrease in cerebral glucose uptake because of slow wave sleep, and a reduction in peripheral glucose utilization (11-13). During the later part of the night, glucose tolerance begins to improve, and, glucose levels progressively decrease towards morning, indicating increased glucose uptake partly because of reduced slow wave sleep and increased rapid eye movement (REM) sleep. These effects of sleep on glucose regulation can also been observed when the sleep period occurs during daytime (14).

Sleep Duration / Sleep Disturbance and Glucose Homeostasis

The duration of sleep is actually determined by individual and social behavioral patterns. Voluntary sleep curtailment to the minimal duration is highly prevalent in the modern society with busy life. Surveys conducted by the National Sleep Foundation in the United States have documented that the proportion of young adults having less than 7 hours of sleep per night has increased from

From the Deptt. of *G Medicine and Director, Govt Medical College, Srinagar- Kashmir- J&K India
Correspondence to : Dr. Waseem Qureshi, Physician Specialist Director, Govt Medical College, Srinagar- Kashmir- J&K India

16% in 1960 to 37% in 2002. Also, over 30% of middle-aged men and women report sleeping less than 6 hours per night (15,16). Voluntary sleep curtailment can cause decrease in sleep quantity, whereas chronic sleep disorders such as insomnia and SDB can affect both sleep quantity and quality, which may lead to disturbed glucose homeostasis (17). The proposed mechanism will be elaborated in below sections.

Research Backup & Review of Relevant Literature

The present write up is based on several studies, both animal and human-based, demonstrating association between sleep disturbances and occurrence of diabetes and a brief account is described here.

Laboratory Studies

Rechtschaffen and co-workers studied rats over a period of 6 years from 1983. They subjected rats to prolonged total sleep deprivation and were unable to show elevated fasting glucose levels despite a marked increase in food intake by the rodents(18,19). However, in 1993, Van Helder and co-workers found that total sleep deprivation in humans resulted in decreased glucose tolerance or increased food intake (20). A landmark study published in 2004, evaluating the effect of short-term partial sleep deprivation on glucose homeostasis subjected 11 young, healthy and lean men to sleep restriction of 4 hours per night over 6 days followed by 7 days of sleep extension of 12 hours per night. After 6 days of sleep restriction, evidence of impaired glucose tolerance was seen. Leptin levels were found to decrease and sympathetic nervous system activity was increased (21). During the same period by the same investigators 12 healthy men were studied and sleep curtailment was limited to 2 days. Despite a shorter duration of sleep deprivation, evidence of impaired glucose tolerance was again observed (22).

Observational and Epidemiologic Studies

Several studies have demonstrated the relationship between the amount or quality of sleep and glucose tolerance. The Sleep Heart Health Study (SHHS) published in 2004, confirmed the diagnosis of OSA objectively with unattended home polysomnography and found an independent association between OSA and glucose intolerance in a subset of 2656 patients10. In a Swedish study published in 2005, men who experienced short duration of sleep were found to have increased incidence of diabetes in a 12-year follow up (23).

Longitudinal Cohort Studies

Several such studies have demonstrated the occurrence of new incident diabetes on longitudinal basis in patients with SDB/OSA. In Sweden and the United States, middle aged men and women, respectively, have been followed-up for 10 years or more, and snoring at baseline was found to be associated with increased incident diabetes (24,25).

Observational Clinical Studies

Several studies with large sample sizes have more consistently reported a positive independent association between SDB, insulin resistance and glucose intolerance (26-27). In 270 Chinese subjects who had polysomnograms in the sleep laboratory, insulin resistance indicated by the homeostasis pattern assessment of fasting insulin and glucose measurements, was independently predicted by obesity, and, to a lesser extent AHI and insulin resistance was a determinant of hypertension (28). In 2006, a study in the United Kingdom assessed the risk of OSA in 1682 men who had type 2 diabetes using a survey followed by overnight oximetry in 240 men selected from groups considered to be at high or low risk of OSA. The study found that 23% of the men who had type 2 diabetes had OSA, and that OSA was significantly associated with DM9. More recently in 2009 a cross-sectional, clinic-based study published from Canada by Ronksby and co-authors had 2149 patients who were subjected to ambulatory monitoring using Remmers Sleep Recorder in some, whiles in others polysomnography was conducted. The overall prevalence of DM was 8.1% which had statistically significant ($p<0.01$) selection with the severity of OSA (6).

There are several other large sample studies showing positive and independent relation between OSA and the development of DM. The description of these studies is beyond the capacity of this article.

Mechanism of Development of Obesity due to OSA

In the study published in 2004 (22), it was observed that 2 days of sleep curtailment led to higher glucose levels, lower insulin levels, and a 30% of increase in appetite for high calorie density carbohydrates. It was also found that the anorexigenic hormone, leptin decreased by 18% and the levels of orexigenic factor ghrelin a stomach derived peptide that stimulates appetite increase by around 28%. Other contributory factors for the development of obesity due to SDB include more time to eat and decreased expenditure of calories. Overall, the sleep disturbance can lead to alterations in glucose homeostasis adversely, affect appetite and hunger, and ultimately increase the risk for obesity and type-2 diabetes (2,29).

Mechanisms of Development of Diabetes due to Sleep-Disordered Breathing

The mechanisms behind alterations in glucose homeostasis due to SDB are multifactorial and are described below:

i.) Besides decreased cerebral glucose metabolism, a reduction in insulin release occurs, probably because of increased sympathetic nervous activity at the level of pancreatic beta-cells. Also, alteration in the secretary profiles of the counter-regulatory hormones may also contribute to the disturbed glucose homeostasis, causing increased levels of growth hormone and even cortisol during night (11,30).

Enhanced sympathetic activity has also been shown consistently in OSA, reflected by microneurography of skeletal muscles or increased catecholamines in plasma or urine. The increased catecholamines and cortisol lead to insulin resistance and beta-cells dysfunction with eventual glucose intolerance and development of type2 DM (31,32)

ii.) Although oxidative stress is considered a pathogentic mechanism in DM, increased oxidative stress has been demonstrated in subjects having OSA (33,34)

iii.) OSA is believed to pose chronic stress caused by recurrent intermittent hypoxia and cerebral arousals. The occurrence of recurrent sleep fragmentation and disrupted sleep architecture also lead to sleep loss. These adverse physiologic effects may trigger downstream mechanisms that promote insulin resistance or glucose intolerance. Again, several studies have demonstrated magnitude of sympathetic activation corresponding with severity of hypoxemia in OSA (35,36).

iv.) Adipose tissue, particularly abdominal fat, is a rich source of adipokines and cytokines that influence insulin sensitivity. SDB may modulate the expression and secretion of these inflammatory mediators from fat and other tissues. Several studies have revealed OSA patients having elevated levels of TNF-alpha and interleukin-6, the cytokines that are antagonistic to the action of insulin. (37,38). In future, more adipokines and cytokines need to be explored for their role in glucose metabolism in OSA.

v.) As mentioned above, OSA leads to decreased levels of leptin and increased levels of ghrelin, leading to increased hunger and contribution to development of obesity which further aggravates OSA (22).

Treatment Strategies

There is now enough evidence available to support that treatment of OSA in patients with diabetes leads to improvement of the disease and decreases their insulin requirements as well (7,39). More recently, several studies documented a positive treatment effect of OSA on insulin resistance and diabetic control, even within 2 nights of treatments with continuous positive airway pressure (CPAP), and the effect was sustained after 3 months of therapy (40). In another study treatment of OSA with CPAP reduced morning postprandial glucose values, and, those who had worse initial glycemic control showed a significant decrease in HbA1C, similar were the findings in another study of 38 patients with severe OSA where treatment with CPAP for 3 weeks showed a decrease in insulin resistance and increase in insulin like growth factor (IGF-1), compared with controls who did not undergo treatment (41). However, contrary to these report one study suggested that short-term CPAP therapy has no significant improvement on glucose metabolism in patients with OSAHS (42).

Future Suggestions

On the basis of the published data we conclude that OSA has a definite link with alterations in glucose metabolism and occurrence of diabetes and obesity. In fact, the interaction among the rising epidemics of obesity, OSA and DM are likely to be complex and involve multiple pathways which will be more clear in future research. A better understanding of the relationship between OSA and type 2 DM may have important public health implications. As per latest recommendations of 2008 (43), individuals diagnosed with DM should be screened for OSA, particularly when witnessed apneas, heavy snoring or daytime sleepiness is present. This will go a long way in better diagnosis and management of these disorder in future.

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