ORIGINAL ARTICLE

OBSTRUCTIVE SLEEP APNOEA: A PREDICTOR OF ABNORMAL GLUCOSE METABOLISM

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Background: Obstructive sleep apnoea can be considered as a hidden killer in our society due to lack of awareness and research, despite its multiple comorbidities and complications like diabetes, cardiovascular diseases and sudden deaths. Studies are showing conflicting results for relationship of apnoea and glucose metabolism. The objective of this study was to explore a possible association between obstructive sleep apnoea and glucose metabolism in our local population**. Methods:** Potential case subjects were scrutinized from Sleep laboratory. Verbal and written informed consent, physical examination, history and Epworth sleep scale score calculation was carried out. After overnight polysomnography, 50 confirmed sleep apnoea subjects were selected. 50 matched controls, without any sleep related complain were selected after informed consent, history and physical examination. Fasting blood sample was collected from all. Blood sugar levels were compared in both groups. Comparison was also done with severity of apnoea in mild, moderate and severe apnoea patients. **Results:** The mean fasting blood sugar was significantly higher in cases (p=0.007). Frequency of population with impaired glucose metabolism was also significantly higher in OSA group (p=0.001). Disturbed glucose metabolism was also found to be associated with severity of apnoea, it was 32% in controls while 50%, 76.5% and 61.9% in mild, moderate and severe apnoea respectively. **Conclusions:** Our findings suggest that obstructive sleep apnoea is associated with a higher disturbance in glucose metabolism; it is also associated with severity of OSA in our population.

Keywords: Glucose metabolism, Obstructive sleep apnoea**,** Sleep

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INTRODUCTION

Sleep in not just the absence of wakefulness or decrease in brain activity but a regulated process which is accompanied by different autonomic and cardiovascular regulatory changes in different stages of sleep. Most of sleep related breathing disorders (SRBDs) are relatively benign and the affectees do not require medical intervention. However obstructive sleep apnoea (OSA), which is the most prevalent of all SRBDs, is a serious condition which requires early diagnosis and medical intervention to prevent complications as it is related with multiple co-morbidities.[1]

Obstructive sleep apnoea has drawn more attention in recent years affecting large number of people worldwide with an incidence of at least 3–7% in adult males and 2–5% in adult females[2] whereas no prevalence date is available for Pakistani population. Some studies considered it as the most common respiratory disorder, with recent data from the United States and Europe, in between 14% and 49% in middle-aged men.[3] These prevalence values are much higher if asymptomatic persons are included. It is assessed that majority of OSA patients go unrecognized in our community, as it is a disorder usually recognized by others who observe the person during sleep.

OSA is a condition with repetitive collapse of the upper airways during sleep for at least 10 seconds accompanied by decreased blood oxygen saturation and excessive day time sleepiness (EDS). Severity of the disorder is characterized by the number of apnoeas and hypopnoea episodes per hour of sleep which is termed as Apnoea-Hypopnoea Index (AHI).[2] Repetitive events of apnoea and hypopnoea with blood hypoxia and hypercapnoea in OSA, impose substantial adverse effects on multiple organ systems specially related to metabolic and neurocognitive health and leads to high morbidity and mortality in OSA patients. Close relationships between sleep regulatory mechanisms and autonomic nervous system (ANS) indicates that OSA can lead to alterations in ANS activity, metabolic abnormalities and may contribute to the development of abnormal glucose metabolism.[4,5]

Research evidences over the last two decades has shown that OSA is linked with insulin resistance (IR), glucose intolerance and type 2 diabetes.[5] An Electrocardiogram-based Sleep Spectrogram study showed that SRBD is independently related to glucose intolerance, impair insulin sensitivity and type 2 diabetic mellitus (T2DM) due to the presence of sleep

fragmentation.[6] A cross-sectional analysis, carried out in 118 non-diabetic subjects, described that SRBDs are responsible for a delayed decline in blood glucose levels after a glucose injection hence showing decreased insulin sensitivity.[7] Sleep Heart Health Study (SHHS) also recommended that relationship of OSA with insulin resistance (IR), glucose intolerance and T2DM is independent to obesity.[8] A population-based study carried out in six research centres in United states on four ethnic groups has reported a significant association of moderate to severe OSA with abnormal fasting glucose in African Americans, independent of sleep duration and obesity.[9] Patients with severe OSA have five times more chances to develop diabetic mellitus in comparison with general population.[10]

In Pakistan, there are limited research studies on OSA and most of them are questionnaire based. We have mentioned about high frequency of metabolic syndrome and disturbance in lipid metabolism in our OSA population in our previous studies.[11,12]

In the present era of changes in life style, when there is continuous increase in OSA prevalence as reported from western and some Asian countries with no report from Pakistan, demands conduction of research in our population. Many studies have raised the potential influence of ethnicity on the metabolic sequelae of OSA which also showed the importance of research for effect of OSA on glucose metabolism in our population. In the present study, fasting blood glucose (FBS) was observed in OSA subjects and in age, gender and BMI matched controls.

MATERIAL AND METHOD

This cross sectional study was conducted at Sleep Laboratory and Polysomnography Department, Dow University of Health & Sciences, Karachi for the period of two years.

The approval of this research study was taken by the ethical review board of the university. The study population was comprised of 50 patients with OSA (aged between 30–65 years) and 50 age, sex & BMI matched controls without OSA. A questionnaire had been designed and approved by the university to record all related information like age, sex, anthropometric measurements (BP, BMI, neck, waist and hip circumferences), Epworth sleep scale (ESS) score, specific question to evaluate socio-economical status, physical activity, medical and surgical history and medication.

Subjects who were referred to the sleep lab for polysomnography (PSG) usually for symptoms of excessive daytime somnolence, snoring and witnessed apnoea were our potential candidates. All potential candidates were selected after taking oral and written informed consent, complete physical examination and calculation of ESS score to confirm their excessive day time sleepiness (EDS). ESS score tells us about presence of excessive day time sleepiness and chances of having sleep apnoea if the score is more than 9.

All potential cases went through full night polysomnography under continuous monitoring by a sleep lab technician. A small video camera was present in the sleep room for observation, while a video monitor and the computer screen was present in a separate room that displays all the data second by second. After Polysomnography, they were classified as mild (AHI=5–15), moderate (AHI= 15–30) and severe apnoea (AHI= >30) subjects.[5] Participants had not been allowed to eat anything until the completion of test.

Age, sex and BMI matched subjects, without any sleep related complain and ESS score less than 9 were selected from DUHS employees and from community as our control group. They were gone through informed consent, history and physical examination. These control subjects were asked to give fasting blood sample after comfortable night sleep.

If person was a diagnosed case of diabetes or have been taking hypoglycaemic medicine then we included him/her, as a subject with disturbed glucose metabolism. BMI was classified as WHO recommendations for Asia Pacific Region.[13] Fasting blood sugar (FBS) was determined by using spectrophotometric method. Some persons also gave their FBS readings on glucometer. Disturbed glucose metabolism was considered if FBS was ≥100 mg/dl or person was already on hypoglycaemic medications.

RESULTS

Mean ESS score was 12.84±4.2 in cases and 4.52±1.82 in controls. The mean of AHI for OSA group was 32.795±22.7 while it was considered as Zero for controls as they had no sleep disturbances. Age, anthropometric measurements, ESS score and mean FBS of cases and controls are mentioned in Table-1.

Mean FBS (mg/dl) was 113.30±22.44 in cases and 98.42±30.91 in controls showing significant difference in both groups (p=0.007). Subjects who were already taking hypoglycaemic medicine or had FBS≥100 mg/dl were 64% (n=32) in cases and 32% (n=16) in controls. So frequency of population with impaired glucose metabolism was significantly higher in OSA group than in the controls (p=0.001). Descriptive analysis in different OSA categories showed 32% population in controls, while 50%, 76.5% and 61.9% population in mild, moderate and severe apnoea groups respectively, were with high FBS/ taking hypoglycaemic medicine (Table-3). These results are indicating association of impaired glucose metabolism with severity of apnoea.

Table-1: Mean baseline characteristics among subjects with and without Obstructive Sleep Apnoea

Baseline characteristics	Controls	Cases	*p*
Age (Years)	47.04 (44.7-49.29)	49.42 (47.21-51.63)	0.133
Height (m)	1.65 (1.63-1.68)	1.67 (1.64-1.71)	0.405
Weight (Kg)	83.12 (78.37-87.87)	89.22 (84.20-94.24)	0.079
BMI	29.89 (28.37-31.47)	31.98 (30.13-33.83)	0.087
Neck circumference (m)	0.38 (0.37-0.39)	0.39 (0.38-0.41)	0.101
Waist circumference (m)	1.04 (0.99-1.08)	1.10 (1.04-1.16)	0.086
Hip circumference (m)	1.11 (1.07-1.15)	1.17 (1.12-1.21)	0.093
Waist to Hip ratio	0.92 (0.9-0.94)	0.94 (0.90-0.97)	0.343
Fasting Blood Glucose (mg/dl)	98.42 (89.63-107.21)	113.30 (106.92-19.68)	0.007*

*Significant

Table-2: Frequency distribution of normal and high fasting blood glucose subjects in cases and control (n=100)

Categories with normal and high FBS	Control n (%)	Case n (%)	Total	*p*
Normal FBS/No Anti Diabetic Medicine	34 (68.0)	18 (36.0)	52 (52.0)	0.001*
High FBS/Anti Diabetic Medicine	16 (32.0)	32 (64.0)	48 (48.0)	

*Significant

Table-3: Number and percentage of subjects in mild, moderate and severe OSA groups with normal and abnormal fasting blood glucose level

Categories with normal and high FBS	OSA CASES			Total in Case group
	Mild Apnoea (AHI 5–15) n (%)	Moderate Apnoea (AHI 15–30) n (%)	Severe Apnoea (AHI >30) n (%)	
Normal FBS or No diabetic	6 (50)	4 (23.5)	8 (38.1)	18 (36.0)
High FBS Or Diabetic	6 (50)	13 (76.5)	13 (61.9)	32 (64.0)
Total	12 (100)	17 (100)	21 (100)	50 (100)

DISCUSSION

We found positive linear relationship between frequency of hyperglycaemia and OSA severity. The mean FBS value and frequency of population with elevated FBS were significantly higher in OSA group. The percentage of patients with elevated FBS/hypoglycaemic medicine was directly associated with the severity of OSA. In both groups mean BMI was not significantly different. These findings suggest that in OSA patients, mechanisms other than obesity are playing their role in the pathophysiology of the disturbed glucose metabolism.

A number of studies conducted on various populations have suggested relationship between insulin resistance (IR) and OSA. On the other hand some studies couldn't get significant results in this regard.[14] A study from Hong Kong documented an association between OSA and IR in both obese and non-obese.[9] In another study Japanese subjects showed higher FBS, fasting plasma insulin and homeostasis model assessment of insulin resistance (HOMA-IR) levels in severe OSA patients in comparison with mild and moderate OSA patients. They concluded that association of OSA with IR is independent of obesity.[15] A study from Han Chinese subjects showed association of OSA with impairment in glucose tolerance and pancreatic β-cell function. The study showed 25.4%, 44.6% and 54.5% subjects with glucose metabolic disorders in control, mild to moderate and severe OSA groups respectively ($p<0.05$) based on oral glucose tolerance-insulin releasing test (OGTT-IRT) and HbA1c serum levels.[16]

The pathophysiological mechanism for the relationship of OSA and abnormal glucose metabolism is not clearly understood. Presence of pro-inflammatory state, production of reactive oxygen species (ROS), elevated sympathetic tone, and change in hypothalamus-pituitary-adrenal axis found in OSA patients, are putative mechanisms proposed for this association.[17] Studies also found that beta cells of pancreas are highly sensitive to hypoxia. Moderate to severe apnoea enforce an excessive functional demand on pancreatic beta-cell, followed by exhaustion and impairment in their secretary capability over time.[18] Loss of proper sleep would promote reduction in glucose tolerance secondary to decrease in brain glucose utilization.[19] According to some studies, Intermittent Hypoxia (IH) present in apnoea can be considered as an important link between OSA with altered glucose metabolism.[5] IH could impose harmful effects on glucose metabolism by augmenting sympathetic nervous system activity, systemic inflammation, change in counter-regulatory hormones and by directly inducing injury to pancreatic beta cells.[20]

Another study proposed that it is about increased release of growth hormone (GH), ghrelin as well as evening release of cortisol. Elevated GH concentration causing insulin resistance in muscle cells decreased glucose uptake and increased blood glucose levels. Elevated evening cortisol level is also known to cause decreased insulin sensitivity on the following morning and further impairment in glucose tolerance.[21] These observations of fluctuations in hormonal circadian rhythm could impose deleterious impact on glucose metabolism.

The role of inflammatory cytokines like TNF-α and IL-6 have been also implicated in glucose metabolism abnormalities in OSA patients. It is postulated that IH and night-time oxyhaemoglobin desaturation produces inflammatory cytokines and reactive oxygen species (ROS) which in turn stimulates IR and chronic metabolic fluxes. Rabinovitch *et al*[22] demonstrated that elevated levels of these cytokines are responsible to increase apoptosis in pancreatic β-cell as

well as in primary islet cells. ROS can also be assigned as a contributor for β-cell dysfunction and apoptosis. According to one more study higher level of IL-6 is an independent predictor for future type 2 diabetes.[23] A study demonstrated that these cytokines can cause insulin resistance by inhibiting insulin signal transduction.[24] Thus it is postulated that higher levels of inflammatory cytokines in OSA patients could lead to disturbance in glucose metabolism. An improvement in insulin sensitivity and HbA1c in majority of OSA subjects following continuous positive air pressure (CPAP) therapy for their OSA, further confirmed the relationship of OSA and glucose intolerance.[25]

Glucose disturbance and insulin resistance are complex metabolic defects that most likely have several etiological factors. Presence of glucose intolerance in our OSA subjects represent considerable risk factors for the development of diabetes, its related complications and CVDs.

CONCLUSION

Our research suggested an association of obstructive sleep apnoea with abnormal glucose metabolism in our local population. It could provide clinicians a potential targets to lifestyle and pharmacological interventions. Our study is highlighting the need for investigating the contribution of sleep disorders to health disparities.

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