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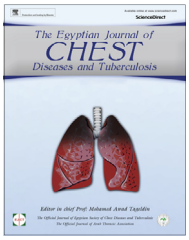

REVIEW

Insulin resistance in obstructive sleep apnea

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KEYWORDS

OSA;
Obesity;
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Abstract *Introduction:* OSA is a common condition that is characterized by intermittent and recurrent pauses in respiration results in multiple cycles of hypoxia/reoxygenation with an increased production of reactive oxygen species (ROS).

Aim of work: Is to assess serum insulin level and insulin resistance in obese patients with and without OSA.

Subjects and methods: Study was performed on 51 obese subjects who had been referred to the Chest Department of Kasr Alaini Hospital with clinical suspicion of OSA in order to perform polysomnography. They were classified into two groups; cases: consist of 33 obese patients who were diagnosed as obstructive sleep apnea (OSA) and controls: consist of 18 obese subjects, without OSA as a control group. The two groups were subjected to polysomnographic study, serum insulin by ELISA and assessment of insulin resistance by calculation of HOMA index.

Results: There was statistically highly significant increase in Epworth sleepiness scale (ESS) among cases compared to controls. As regards the polysomnographic data, there was statistically highly significant increase in AHI, desaturation index and duration of desaturation $<90\%$ among cases compared to control subjects. Regarding minimal O_2 sat% and average O_2 sat% were lower in cases than in the control subjects and this reduction was statistically significant. There was statistically highly significant increase in serum insulin, HOMA index among cases as compared to controls.

Conclusion: Insulin resistance in OSA is related to sleep associated hypoxemia and hypoxic stress.

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Introduction

The association of OSA and glucose intolerance/insulin resistance has been consistently shown in numerous studies involving different ethnicities and study design [1]. It was shown that sleep related hypoxemia was associated with glucose intolerance independently of age, sex, BMI and waist circumference. OSA severity was also associated with the degree of IR (insulin resistance) after adjustment for obesity [2].

Most studies have focused on the impact of SDB on insulin sensitivity/resistance, which reflect glucose utilization in peripheral tissue in response to insulin. Pancreatic β-cells, like any other tissues in the body, are also subject to the detrimental effects of sleep apnea and intermittent hypoxia. Other than a progressive reduction in insulin sensitivity with increasing severity of SDB, the disposition index, a measure of pancreatic b-cell function, was also reduced in those with moderate-to-severe OSA. The latter finding suggested that insulin secretion may be affected by OSA [3].

Subject and methods

The present study was performed on 51 obese subjects who had been referred to the Chest Department of Kasr Alaini Hospital for clinical assessment.

The included subjects were classified into two groups:

- Cases: consist of 33 obese patients who were diagnosed as obstructive sleep apnea (OSA) based on both clinical and polysomnographic criteria (AHI $\geqslant$ 5 events/h).
- Controls: consist of 18 obese subjects, without OSA as a control group. They were clinically free from any known diseases.

Inclusion criterion; subjects with BMI > 30 kg/m^2.
Exclusion criteria:

1- Known cases of D.M., hypertension.
2- History of cardiac troubles.
3- Presence of chest symptoms

Study design

The 2 groups were subjected to the following:

1- Full history taking with special emphasis on key symptoms of OSA.

2- Epworth sleepiness scale (ESS): The patients were asked, to evaluate sleepiness (how likely are you to doze off or fall asleep in the following situations):

1. Sitting and reading.
2. Watching television.
3. Sitting inactive in a public place (e.g. theater).
4. As a car passenger for an hour without break.
5. Lying down to rest in the afternoon.
6. Sitting and talking to someone.
7. Sitting quietly after lunch without alcohol.
8. In a car, while stopping for a few minutes in traffic.

The following scale was then used to choose the most appropriate number for each situation:

0 = would never doze.
1 = slight chance of dozing.
2 = moderate chance of dozing.
3 = high chance of dozing.

Interpretations of Epworth sleepiness scale [4]:

a. Supernormal (if ESS 0–5).
b. Normal (if ESS 5–10).
c. Sleepy (if ESS 10–15).
d. Very sleepy (if ESS 15–20).
e. Dangerously sleepy (if ESS > 20).

3- Full clinical examination.

4- Anthropometric measurements: All patients underwent comfort evaluation of anthropometric measures including: body weight, height, body mass index (BMI in kg/m), weight waist and hip circumferences, waist/hip ratio and neck circumference.

National Institutes of Health, 2000 [5] had classified obesity according to BMI into:

- Class I obesity (includes cases with BMI 30.0–34.9)–
  Class II obesity (includes cases with BMI 35.0–39.9)–
  Class III obesity (includes cases with BMI > 40.0).

5- Polysomnographic study: (8 h per night) with detailed analysis of the recorded data. Before the study, patients were advised to avoid tea and coffee intake or any other drugs that may have influence on the quality of sleep as sedatives, hypnotics and tranquilizers.

1. Patients presented to the Sleep Laboratory Unit in chest department of Cairo University Hospital 1 h before their usual bed time to get familiar and adapt with the

environment. We provided them with full explanation of the nature and aim of polysomnography. The duration of polysomnographic monitoring was about eight continuous hours.

2. Patients were connected to SOMNOscreen™ plus (Cardio-Respiratory Screening) which is computer based high technology polysomnography that included:

- Pulse oximetry applied to the index finger to detect arterial oxygen saturation (SaO_2): O_2 desaturation index (/h): number of O_2 desaturation per hour of sleep, minimal nocturnal SaO_2 (%) and time in which $SaO_2 < 90\%$ (as a percent from total sleep time).

3. A microphone applied on the neck beside the larynx to detect snoring.
4. Heart rhythm is monitored with a single lead ECG: to detect arrhythmia index which is the number of cardiac arrhythmias per hour of sleep.
5. Oronasal airflow using thermal sensors and nasal pressure transducer.
6. Chest and abdominal movements recording using 2 separate belts to detect the effort.
7. Leg movements are recorded via anterior tibialis electromyogram.
8. From recording of sleep study we detect.
9. Apnea: defined by the cessation of airflow for a minimum of 10 s, with the oral thermistor providing the most accurate detection of an apnea. An apnea is further classified as obstructive, central or mixed based on the assessment of respiratory effort during the event [6].
10. Hypopnoeas: are generally classified only as obstructive events. Hypopnoeas can be scored using various definitions although most commonly they are characterized by at least a 30% reduction in airflow in association with a 3% or 4% oxygen desaturation [6]. A desaturation is scored when the following two parameters are met; minimum drop required is 4% (the minimum decrease in oxygen level to score a desaturation). Minimum duration required is 10 s.
11. AHI: refers to the number of apneas and hypopnoeas per hour of sleep.
12. Snoring index: the number of snoring events per hour of sleep.
13. Arrhythmia index: number of cardiac arrhythmias per hour of sleep.
14. The severity of sleep-related obstructive breathing events will be rated as follows: mild: 5–15 events/h; moderate: 15–30 events/h; and severe > 30 events/h [7].

6- Laboratory examination: Ten milliliter of fasting venous blood, at least 12 h fasting, was collected for estimation of FBS.

According to American Diabetes Association, 2008, [8] the level of FBS can be classified into:

- Normal < 100 mg/dL (5.6 mmol/L).
- Impaired fasting glucose: 100–125 mg/dL (5.6–6.9 - mmol/L).
- Provisional diagnosis of diabetes ⩾126 mg/dL (7 - mmol/L).

7- Serum Insulin: the ab100578 Human Insulin ELISA (Enzyme-Linked Immunosorbent Assay) kit is an in vitro enzyme-linked immunosorbent assay for the quantitative measurement of human insulin in serum and plasma.

8- Assessment of insulin resistance: The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and beta-cell function .The HOMA approach has been widely used in clinical research to assess insulin sensitivity. Rather than using fasting insulin levels, the product of the fasting concentrations of glucose (expressed as milligrams per deciliter) and insulin (expressed as micro-units per milliliter) is divided by a constant (Cutfield et al., 2003) [9].

HOMA-IR = FBS (mg/dl) × Serum insulin (μIU/ml)% 405.

HOMA cutoff point for diagnosis of insulin resistance is > 2.5 which is valid for adults (Mehmet et al., 2005) [10].

Statistical analysis of the results

Data were statistically described in terms of mean ± standard deviation (±SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student *t* test for independent samples in comparing normally distributed and Mann Whitney *U* test for independent samples when not normally distributed. For comparing categorical data, Chi square (χ) test was performed. Exact test was used instead when the expected frequency is less than 5. Correlation between different variables was done using Pearson moment correlation equation for linear variables. *p* values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for MicrosoftWindows.

Results

The results are shown in Tables 1–9.

Discussion

The control group included 14 females (77.8%) and 4 (22.2%) males, while cases included 10 females (30.3%) and 23 males (69.7%) Table 1. This result is in agreement with Nakayama-Ashida et al. in 2008 who stated that OSA syndrome is more common in adult males compared to adult females [11].

In the present study the mean age of cases was 52.12 and SD ± 11.48 which was higher than controls (mean age 44.83

Table 1 Sex distribution; statistical comparison between cases and controls.

			Group		Total
			Cases	Control	
Sex	Females	Count	10	14	24
		% within group	30.3%	77.8%	47.1%
	Males	Count	23	4	27
		% within group	69.7%	22.2%	52.9%
Total		Count	33	18	51
		% within group	100.0%	100.0%	100.0%

Table 2 Age distribution; statistical comparison between cases and controls.

Group		Age (years)
Cases	*N*	33
	Mean	52.12
	Std. deviation	11.48
Control	*N*	18
	Mean	44.83
	Std. deviation	12.70

and SD ± 12.70) Table 2. This is in agreement with Peppard et al. in 2000 who reported increase in the prevalence of OSA with age that could not be explained by other risk factors such as obesity [12].

In the current study the BMI mean value among cases was 42.82 and SD ± 7.69, denoting that most of our patients were considered as class 3 obesity Table 3.

This is in agreement with Shelton et al. in 1993 who stated that obesity is believed to predispose to OSA because of mass loading to the upper airway of the neck [13].

Also Strohl and Redline, in 1996 stated that excess body weight is a major risk factor for snoring and sleep apnea and that 70% of patients with OSAS are overweight [14].

However the mean value of BMI among controls was 44.33 and SD ± 5.68, which was higher than cases and did not reach any statistical significance Table 3.

Lecube et al. in 2010 found that not all subjects who are obese or having a large neck circumference suffer from sleep apnea, supporting our result [15].

As regards to other anthropometric measurements we found that W/H ratio (Waist/Hip ratio) mean value among cases was 3.75 and SD ± 15.66 which was higher than controls (mean value was 0.93 and SD ± 0.07). The mean value of WC (Waist circumference) among cases was 138.61 and SD ± 12.74 which was higher than controls (mean value was 132.94 and SD ± 16.40) and regarding NC (Neck circumference) the mean value among cases was 47.03 and SD ± 5.03 which was also higher than controls (mean value was 44.78 and SD ± 5). The differences between cases and controls regarding these anthropometric measurements were statistically insignificant Table 3.

Mortimore et al. in 1998 found that the predictive value of other anthropomorphic variables related to body weight, such as waist circumference, waist-to-hip ratio, is generally lower in OSA except in extreme cases, supporting our results [16].

Table 4 Statistical comparison between cases and controls as regards Epworth sleepiness scale (ESS).

Group		Age (years)
Cases	N	33
	Mean	17.61
	Std. deviation	6.07
Control	N	18
	Mean	8.78
	Std. deviation	2.43
p-Value = 0.000*		

The mean value of Epworth sleepiness scale (ESS) among cases was 17.61 and SD ± 6.07 compared to controls with the mean value of 8.78 and SD ± 2.43. This increase in Epworth sleepiness scale (ESS) among cases compared to controls was statistically highly significant Table 4.

This is in agreement with Banamah, in 2010 who studied 27 patients with OSA and 26 obese subjects without OSA as control group he found highly significant increase in ESS among the patients with OSA in comparison to control subjects [17].

In the present study, there was statistically highly significant increase in AHI, desaturation index and duration of desaturation <90% among cases compared to control subjects. While minimal O_2 sat% and average O_2 sat% were lower in cases than in control subjects and this reduction was statistically significant Table 5.

This is in agreement with results obtained by Kaynak et al. in 2003, who demonstrated that the minimal oxygen saturation point was statistically lower in patients with OSA than controls [18].

Also Nakagawa et al. in 2008 studied 93 patients with OSA and 18 control subjects, they found that AHI, desaturation index, and the percentage of arterial O_2 saturation from pulse oximetry (Sp_{O2}) < 90% were significantly higher and the lowest Sp_{O2} was significantly lower in OSAHS patients than in the control subjects [19].

Concerning the arrhythmia index the current study revealed a higher mean value among cases (25.85 and SD ± 23.04) compared to controls (9.78 and SD ± 13.95) and this difference was found to be statistically significant Table 5.

This result is in agreement with Hoffstein and Mateika, 1994 who analyzed electrocardiographic recording in 458 patients having sleep studies and showed a 58% prevalence of arrhythmias in patients with OSA compared with 42% in

Table 3 Statistical comparison between cases and controls as regards anthropometric measurements.

Group		BMI kg/m	W/H ratio	WC (cm)	NC (cm)
Cases	N	33	33	33	33
	Mean	42.82	3.75	138.61	47.03
	Std. deviation	7.69	15.66	12.74	5.03
Control	N	18	18	18	18
	Mean	44.33	0.93	132.94	44.78
	Std. deviation	5.68	0.07	16.40	5.00
p-Value		0.804	0.450	0.177	0.132

Table 5 Statistical comparison between cases and controls as regarding polysomnographic data.

Group		AHI	Desat. index	Minimal O_2 sat%	Average O_2 sat%	Duration of desat. < 90%	Snoring index	Arrythmia index
Cases	N	33	33	33	33	33	33	33
	Mean	19.23	40.92	68.58	89.76	35.26	236.36	25.85
	Std. deviation	13.98	26.00	17.22	5.33	31.26	148.04	23.04
Control	N	18	18	18	18	18	18	18
	Mean	2.14	8.11	83.61	94.44	5.90	143.47	9.78
	Std. deviation	1.37	9.60	7.94	1.50	9.12	134.11	13.95
p-Value		0.000*	0.000*	0.001*	0.001*	0.000*	0.032*	0.003*

Table 6 Comparison between cases and controls as regarding FBS.

			Group	
			Cases	Controls
FBS	Normal	Count	7	5
		% within group	21.2%	27.8%
	Impaired fasting glucose	Count	12	11
		% within group	36.4%	61.1%
	Provisional diagnosis of diabetes	Count	14	2
		% within group	42.4%	11.1%
Total		Count	33	18
		% within group	100%	100%

Table 7 Statistical comparison between cases and controls as regarding serum insulin level and HOMA index.

Group		Insulin uU/ml	HOMA index
Cases	N	33	33
	Mean	18.77	5.93
	Std. deviation	4.02	2.13
Control	N	18	18
	Mean	9.16	2.43
	Std. deviation	1.60	0.64
p-Value		0.000*	0.000*

Table 8 Correlation between severity of OSA, grade of obesity and FBS (fasting blood sugar) among cases.

		Severity of OSA	Grade of obesity
FBS	Pearson correlation	0.260	0.163
	p-Value	0.144	0.365
	N	33	33

Table 9 Correlation between severity of OSA, grade of obesity and serum insulin level and HOMA index among cases.

		Severity of OSA	Grade of obesity
Insulin	Pearson correlation	−0.051	0.124
	p-Value	0.777	0.491
	N	33	33
HOMA index	Pearson correlation	0.203	0.054
	p-Value	0.257	0.765
	N	33	33

non-apneic, and also they found that most arrhythmias occur in those with AHI > 40/h [20].

In the present study, there was statistically significant increase in snoring index among cases (236.36 and SD ± 148.04) than control subjects (143.47 and SD ± 134.11) Table 5.

This is in agreement with Hudgel, in 1986 who stated that snoring is the primary symptom of nearly all patients with sleep apnea [21].

Also our result is matched with Viner et al. in 1991 who stated that hat snoring is a hallmark of OSA [22].

A comparison between cases and controls as regarding FBS shows that among cases 42.4% had Provisional diagnosis of diabetes, 36.4% had Impaired fasting glucose and 21.2% had normal FBS. Whereas among controls only 11.1% had Provisional diagnosis of diabetes, 61.1% had Impaired fasting glucose and 27.8% had normal FBS Table 6.

Also we found statistically highly significant increase in serum insulin level among cases (mean value was 18.77 and SD ± 4.02) as compared to controls (mean value was 9.16 and SD ± 1.60). Regarding HOMA index (for insulin resistance) we found statistically highly significant increase in the mean value among cases (5.93 and SD ± 2.13) compared to control subjects (mean value was 2.43 and SD ± 0.64) Table 7.

This is in agreement with Ip et al. in 2002 who investigated the relationship between sleep-disordered breathing and insulin resistance, indicated by fasting serum insulin level and insulin resistance index based on the homeostasis model assessment method (HOMA-IR). Among a total of 270 consecutive subjects, 197 non-diabetic males referred for

polysomnography were included, and 185 were documented to have OSA. They found that OSA subjects were more insulin resistant, as indicated by higher levels of fasting serum insulin ($p = 0.001$) and HOMA-IR ($p < 0.001$) [23].

Also Reichmuth et al. in 2005 demonstrated a significant cross sectional association between OSA and type 2 diabetes for all degrees of OSA, which persisted for moderate-to-severe OSA after adjustment for obesity [24].

In the current study there was insignificant positive correlation between severity of OSA and FBS among cases Table 8.

This result is in agreement with Elmasry et al. in 2001 who reported that patients with OSA tend to have higher levels of fasting blood glucose, and glycosylated hemoglobin, independent of body weight [25].

Also as regarding the grade of obesity there was a positive insignificant correlation between grade of obesity and FBS among cases Table 8.

This result is in agreement with Lam et al. in 2010 who reported that obesity is considered the most common risk factor for a spectrum of glucose disorders ranging from insulin resistance to overt type 2 diabetes mellitus, hypertension, dyslipidaemia and the metabolic syndrome [26].

In our study we found a negative insignificant correlation between severity of OSA and serum insulin level among cases Table 9.

This result is in agreement with Punjabi and Beamer, in 2009 who reported that pancreatic β-cell function was reduced in those with moderate-to-severe OSA. This finding may suggest that insulin secretion may be impaired by OSA [3].

However Elmasry et al. in 2001 reported that patients with OSA tend to have higher levels of serum insulin [25].

In the current study there was a positive insignificant correlation between grade of obesity and serum insulin level Table 9.

This result is matched with Steppan et al. in 2001 who reported a decrease in insulin-stimulated glucose uptake by adipocytes in obese patients and they suggested that hypoxia-induced hormonal reaction was responsible for increased insulin level which was associated with a decrease in insulin sensitivity in the tissues [27].

Conclusions

It was concluded that serum insulin was significantly higher in obese patients with OSA than obese subjects without OSA. Also obese patients with OSA showed more insulin resistance than obese subjects without OSA and that serum insulin and HOMA index could be used as prognostic factors to assess the response following CPAP treatment or Bariatric surgery in patients with OSA, however further researches still need to confirm this fact.

Conflict of interest

None declared.

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