Research Article

Metabolic Disorders in Obstructive Sleep Apnea Patients

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Abstract
Background : Obstructive sleep apnea (OSA) is a common chronic disorder with a prevalence of 2–4% in general with an approximate rate of 14% in men and 5% in women aged (30–70) years respectively [1]**.** OSA is diagnosed according to clinical symptoms and episode of apnea-hypopnea measured via polysomnography (PSG). OSA is a worldwide highly prevalent disease associated with systemic consequences, including excessive sleepiness, neurocognitive dysfunction and daytime performance. The long-term sequelae of OSA lead to cardiovascular, cerebrovascular and metabolic syndrome disorders that lead to premature death if untreated[2]. **Objective:** This study aimed to determine metabolic syndrome comorbidities associated with OSA patients. **Results:** ninety (90) subjects were involved in this study 45 volunteers as a control ,45 patients with OSA (6 mild, 14 moderate, and 25 severe), their ages Mean±SD 57.2±8.9, 33.3% males, and 66.7% females, 24.4% current smoker, 8.9% ex-smoker, and 66.7% non-smoker. BMI was significantly higher among OSA patients than obese and non-obese control groups (P= <0.001). Neck circumference was significantly large among OSA patients than control groups (P= <0.001). Comorbidities as hypertension and DM was significantly high among OSA patients than control groups (p= <0.001*). There was statistically significant increase in thioredoxin among OSA patient more than control non-obese group (P= 0.026*). Also; there was decrease in adiponectin in OSA patients more than control obese and non-obese but in non-significant manner. There was statistically significant decrease in adiponectin with sever OSA more than moderate and mild groups (P= 0.022*). **Conclusion**: OSA is a serious condition that can be diagnosed with polysomnography and is associated with cardiovascular and metabolic comorbidities.
Keywords: Obstructive sleep apnea, metabolic syndrome, cardiovascular diseases, hypertension, diabetes, thioredoxin, and adiponectin.

Introduction
Obstructive sleep apnea (OSA) is defined as the collapse of the upper airway during sleep, causing intermittent hypoxia and sleep fragmentation[3]. It can result in cardiovascular diseases, metabolic dysregulation, and neurocognitive dysfunction [4].

OSA is a common chronic disorder with a rated prevalence of 2–4% in general population and it was believed to be rising continuously with an approximate rate of 14% in men and 5% in women aged 30–70 years[1]. It is higher in patients with obesity, type 2 diabetes mellitus (T2DM) and other cardiovascular disorders[5].

The diagnosis of OSA depends on assessing the risk for OSA with history and physical examination to look for the signs and symptoms of the syndrome such as; snoring, disturbed sleep, daytime sleepiness, decreased libido as well as a history of hypertension (HTN), cardiovascular disease, and diabetes.

A number of out-patient screening questionnaires such as Epworth sleepiness scale (ESS), STOP-BANG questionnaire, and the Berlin Questionnaire etc. help to identify patients with OSA, however gold standard diagnosis is achieved using polysomnography (PSG)[6,7]. Imaging such as magnetic resonance imaging (MRI), computed tomography (CT), cephalometry, and ultrasonography (US) have been used to evaluate UA structures in patients with OSA however, MRI and CT are not widely used for this purpose, due to the expense and radiation exposure [8].

Subjects and methods
Our observational case control study was conducted on 90 subjects (45 patients with confirmed polysomnographic sleep related respire-

tory disorders, 23 obese participants and 22 non obese participants) that attended outpatient chest clinic at cardiothoracic hospital during the period between January 2019 and January 2020.written informed consent was obtained for those invited and agreed to participate in this study.

Inclusion criteria

Adult patients confirmed to have OSA by polysomnography.

Exclusion criteria

- Age less than 18 years old.
- Psychosis.
- Medical disorder as left sided heart failure, liver diseases and renal diseases.
- Any chronic chest disease that may pro-found the degree of hypoxemia and cofounding effect of OSA on polysomno-graphic recorded parameters
- Severe musculoskeletal disorder.
- Any severe surgical problem that interfere with the study.
- Pregnancy.

1- All patients confronted to detailed history taking involving STOP BANG questionnaire, history of associated comorbidities as DM and hypertension.

2- General and local examination involving vital signs, BMI and neck circumference.

3- Retrieved polysomnographic (PSG) data including apnea hypopnea index (AHI), oxygen desaturation index (ODI), Minimum O_2 value and Number of desaturations below 90%.

4- Spirometry was performed using a spiro-meter (ZAN 300, Germany) to exclude associated chronic chest diseases confound-ding the results of current study

5- Laboratory investigations:

- Complete blood count.
- Renal function test.
- Liver function test.
- Random blood sugar.
- Arterial blood gases.

6- Thyroid function tests (TSH, free T3 and free T4).

7- Lipid profile:

They had been made by micro lab 300. Lipids are a group of fats and fat-like substances that are important constituents of cells and sources of energy. It measures the level of specific lipids in the blood.

Two important lipids, cholesterol and triglycerides, are transported in the blood by lipoproteins. Lipoproteins that transport the lipids in the blood are classified by their density into HDL and low-density lipoproteins (LDL).

8- Thioredoxin: made by ELISA (ELABSCIENCE).

9- Thioredoxins are proteins that act as antioxidants by facilitating the reduction of other proteins by cysteine thiol-disulfide exchange[9]. It is a protein playing a protective role against oxidant injury. Serum TRX levels increase in OSAS patients in comparison with healthy controls.

Peripheral venous blood sample was collected from all the study participants. The samples were subjected to centrifugation at 4000 rpm for 20 min and were then equally distributed into aliquots and stored at −20°C till the time of the assay.

10- Adiponectin: made by ELISA (ELABSCIENCE)

Adiponectin is an adipocyte-derived hormone with multiple biological functions [10]. It appears to play a crucial role in protecting against insulin resistance/diabetes and Atherosclerosis, the production of endogenous adiponectin is impaired as an effect of obesity and related pathologies[11]. The normal range of it is between 3.5μg/mL and 22.4μg/mL.

Peripheral venous blood sample was collected from all the study participants. The samples were subjected to centrifugation at 4000 rpm for 20 min and were then equally distributed into aliquots and stored at −20°C till the time of the assay.

Statistical analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 25. Descriptive statistics were done for non-parametric quantitative data by median and interquartile range (IQR), while they were done for categorical data by number and percentage.

Distribution of the data was done by Shapiro Wilk test. Analysis were done for parametric quantitative data between the three groups using One way ANOVA test followed by Post Hoc Analysis between each two groups and for non-parametric quantitative data between the three

groups using Kruskal Wallis Test followed by Mann Whitney test between each two groups.

Analyses were done for parametric quantitative data between the two groups using Independent samples T test and for non-parametric quantitative data between the two groups using Mann Whitney test. Analyses were done for qualitative data using Chi square test (if less than 20% of cells have expected count <5) or Fisher's exact test (if more than 20% of cells have expected count <5).Correlations between different variables were done using Pearson's correlation coefficient. Simple logistic regression analysis of different variables that predict diseases.

ROC curve analysis for calculation of AUC, optimal cutoff point, sensitivity, specificity, PPV, NPV and accuracy of different variables predicting the diseases. The level of significance was taken at (P value < 0.05).

Ethical considerations

The study was approved by Minia University Hospital's Research Ethics Board, Minia University, Egypt.

Results

This observational cross sectional, case control study was carried on 90 subjects,[45] of them had OSA,[23] of them were obese healthy and [22] of them were non-obese healthy selected from patients who sought a medical advice in outpatient chest clinics or in inpatient inwards, cardiothoracic Minia university hospital during the period between January 2019 to January 2020.

In this study.

Table (1): shows that BMI, and neck circumference were significantly higher among OSA patients than control obese and non-obese subjects (P= <0.001*).

Table (2): shows that neck circumference were significantly higher among sever group than moderate and mild groups (P= 0.007*).

Table (3): shows comorbidities associated with OSA as the prevalence of hypertension, DM, and elevated PASP was significantly higher among OSA patients (P= <0.001*, P= 0.005*, and P= <0.001* respectively).

Table (4): shows that there was statistically significant increase in the prevalence of DM among sever OSA patients more than moderate and mild groups (P= <0.001*).

Table (5): shows that there was statistically significant decrease in FVC among OSA patients more than control obese and non-obese subjects (P= <0.001*).

There was also statistically significant incr-ease in ESS among OSA patients more than control obese and non-obese subjects (P= <0.001*).

There was a high statistically significant increase in STOP BANG questionnaire among OSA patients more than control obese and non-obese subjects (P= <0.001*).

Table (6): shows the polysomnographic data of the diseased groups.

It was found that AHI was more in the sever OSA patients than moderate and mild groups (P= <0.001*), average SO2 was less among the sever group than moderate and mild groups (P= 0.010*), minimal SPO2 during the PSG was decreased among the sever group more than moderate and mild groups (P= 0.004*), SPO2 time less than 90% was more in sever than moderate and mild groups (P= 0.020*), and that number desaturations less than 90 was increased among sever group than moderate and mild groups (P= 0.006*).

Table (7): shows that there was statistically significant increase in thioredoxin among OSA patient more than control non-obese group (P= 0.026*).

Also; there was decrease in adiponectin in OSA patients more than control obese and non-obese but in non-significant manner.

Table (8): shows that there was statistically significant decrease in adiponectin with sever OSA more than moderate and mild groups (P= 0.022*).

Table (1): Socio- demographic, and anthropometric measures among the studied groups:

		Control obese (I)	Control non obese (II)	Cases (III)	P value		
		N=23	N=22	N=45			
Age	**Mean±SD**	50.3±9.5	48.3±6.5	57.2±8.9	<0.001*		
					I vs II	**I vs III**	**II vs III**
					0.705	0.007*	<0.001*
Sex	**Male**	12(52.2%)	10(45.5%)	15(33.3%)	0.293		
	Female	11(47.8%)	12(54.5%)	30(66.7%)	**I vs II**	**I vs III**	**II vs III**
					0.652	0.133	0.335
Special habit	**Current**	6(26.1%)	8(36.4%)	11(24.4%)	0.672		
	Ex-smoker	4(17.4%)	2(9.1%)	4(8.9%)	**I vs II**	**I vs III**	**II vs III**
	No smoker	13(56.5%)	12(54.5%)	30(66.7%)	0.707	0.555	0.617
BMI	**Mean±SD**	39.5±3.8	23.8±2	44.4±6.5	<0.001*		
					I vs II	**I vs III**	**II vs III**
					<0.001*	0.001*	<0.001*
Neck circumference	**Mean±SD**	36±2.7	30.5±2.3	46.2±4.3	<0.001*		
					I vs II	**I vs III**	**II vs III**
					<0.001*	<0.001*	<0.001*

BMI= body mass index.

Table (2): Socio- demographic, and anthropometric measures among the diseased groups:

		Mild (A)	Moderate (B)	Severe (C)	P value		
		N=6	N=14	N=25			
Age	**Mean±SD**	53.7±10.3	56.3±10	58.5±7.9	0.454		
					A vs B	**A vs C**	**B vs C**
					0.819	0.465	0.742
Sex	**Male**	1(16.7%)	3(21.4%)	11(44%)	0.296		
					A vs B	**A vs C**	**B vs C**
	Female	5(83.3%)	11(78.6%)	14(56%)	1	0.363	0.187
Special habit	**Current**	0(0%)	3(21.4%)	8(32%)	0.516		
	Ex-smoker	1(16.7%)	1(7.1%)	2(8%)	**A vs B**	**A vs C**	**B vs C**
	Non smoker	5(83.3%)	10(71.4%)	15(60%)	0.556	0.273	0.866
BMI	**Mean±SD**	40.7±4.1	43.2±4.8	45.9±7.4	0.145		
					A vs B	**A vs C**	**B vs C**
					0.690	0.173	0.411
Neck circumference	**Mean±SD**	42.5±2.7	45±2.6	47.8±4.6	0.007*		
					A vs B	**A vs C**	**B vs C**
					0.395	0.012*	0.086

Table (3): comorbidities among the studied groups:

		Control obese (I)	Control non obese (II)	Cases (III)	P value		
		N=23	N=22	N=45			
HTN	Yes No	4(17.4%) 19(82.6%)	0(0%) 22(100%)	26(57.8%) 19(42.2%)	**<0.001***		
					I vs II	**I vs III**	**II vs III**
					0.109	0.002*	<0.001*
DM	Yes No	0(0%) 23(100%)	0(0%) 22(100%)	9(20%) 36(80%)	**0.005***		
					I vs II	**I vs III**	**II vs III**
					---	0.023*	0.025*
PASP	Mean±SD	19±4.1	19.8±3.3	57.1±12	**<0.001***		
					I vs II	**I vs III**	**II vs III**
					0.949	<0.001*	<0.001*

HTN= hypertension; DM= diabetes mellitus; PASP= pulmonary artery systolic pressure.

Table (4): comorbidities among the diseased groups:

		Mild (A)	Moderate (B)	Severe (C)	P value		
		N=6	N=14	N=25			
HTN	Yes	4(66.7%)	8(57.1%)	14(56%)	1		
					A vs B	**A vs C**	**B vs C**
	No	2(33.3%)	6(42.9%)	11(44%)	1	1	1
DM	Yes	0(0%)	2(33.3%)	7(50%)	<0.001*		
					A vs B	**A vs C**	**B vs C**
	No	25(100%)	4(66.7%)	7(50%)	0.642	0.032*	<0.001*
PASP	Mean±SD	52±15.4	57±12.6	58.4±11		0.517	
					A vs B	**A vs C**	**B vs C**
					0.675	0.485	0.939

Table (5): spirometry and sleep questionnaires among the studied groups:

		Control obese (I)	Control non obese (II)	Cases (III)	P value		
		N=23	N=22	N=45			
FEV1	Mean±SD	83.8±8.8	84.9±9.6	57.9±15.5	<0.001*		
					I vs II	**I vs III**	**II vs III**
					0.956	<0.001*	<0.001*
FVC	Mean±SD	90.7±7.4	89.9±8.5	53.2±11.9	<0.001*		
					I vs II	**I vs III**	**II vs III**
					0.967	<0.001*	<0.001*
Ratio	Mean±SD	85.2±7	82.5±6.8	78.1±13.4	0.030*		
					I vs II	**I vs III**	**II vs III**
					0.682	0.030*	0.252
ESS	Median IQR	0 (0-0)	0 (0-0)	17 (15-18)	<0.001*		
					I vs II	**I vs III**	**II vs III**
					0.162	<0.001*	<0.001*
STOP BANG	Median IQR	2 (1-3)	1 (0-1)	7 (7-7)	<0.001*		
					I vs II	**I vs III**	**II vs III**
					<0.001*	<0.001*	<0.001*

FEV1= forced expiratory volume 1; FVC= forced vital capacity.

Table (6): polysomnographic data among the diseased groups:

		Mild (A)	Moderate (B)	Severe (C)	P value		
		N=6	N=14	N=25			
A-H Index	**Median IQR**	12 (5-13.3)	28 (27-29)	67 (54-95)	<0.001*		
					A vs B	**A vs C**	**B vs C**
					<0.001*	<0.001*	<0.001*
					A vs B	**A vs C**	**B vs C**
Average SPO_2	**Median IQR**	90 (87-93)	85.5 (74.3-89.3)	79 (73-85)	0.010*		
					A vs B	**A vs C**	**B vs C**
					0.047*	0.004*	0.168
Minimal SPO_2	**Median IQR**	83 (73.8-86.8)	68 (52.5-79)	52 (48-59.5)	0.004*		
					A vs B	**A vs C**	**B vs C**
					0.029*	0.010*	0.022*
SPO_2 time less than 90	**Median IQR**	54 (31.5-81.5)	93.5 (71.2-96.3)	95.2 (92.5-97)	0.020*		
					A vs B	**A vs C**	**B vs C**
					0.076	0.010*	0.146
Number desaturations less than 90	**Median IQR**	53 (32.3-77.3)	136 (86.5-172.5)	176 (115.5-232.5)	0.006*		
					A vs B	**A vs C**	**B vs C**
					0.017*	0.008*	0.057

AHI= apnea-hypopnea index.

Table (7): Biomarkers, thyroid function and lipid profile of the studied groups:

		Control obese (I)	Control non obese (II)	Cases (III)	P value		
		N=23	N=22	N=45			
Adiponectin	**Median IQR**	2135 (575-5935)	3037.5 (330-5862.5)	1480 (710-3035)	0.214		
					I vs II	**I vs III**	**II vs III**
					0.892	0.123	0.193
Thioredoxin	**Median IQR**	365 (280-447.5)	282.5 (187.5-356.3)	395 (325-490)	0.036*		
					I vs II	**I vs III**	**II vs III**
					0.026*	0.421	0.026*
TSH	**Median IQR**	1.4 (0.4-2.3)		1.7 (0.6-4.3)			
					I vs II	**I vs III**	**II vs III**
							0.288
Free T3	**Median IQR**	3 (3-4)		3 (3-4)			
					I vs II	**I vs III**	**II vs III**
							0.637
Free T4	**Mean±SD**	15.3±2.6		14.7±2.8			
					I vs II	**I vs III**	**II vs III**
							0.431
Cholesterol	**Median IQR**	254 (201.5-328.5)	228 (216.8-273.5)	265 (222-334)	0.443		
					I vs II	**I vs III**	**II vs III**
					0.251	0.618	0.307
TG	**Median IQR**	103 (80-180)	92 (86-123.3)	130 (91.5-214)	0.202		
					I vs II	**I vs III**	**II vs III**
					0.803	0.357	0.062
HDL	**Mean±SD**	45.2±10.6	47.2±6.4	43.1±8.3	0.321		
					I vs II	**I vs III**	**II vs III**
					0.288	0.641	0.672
LDL	**Median IQR**	190 (152-232)	180 (132.8-223)	169 (119-220)	0.339		
					I vs II	**I vs III**	**II vs III**
					0.578	0.161	0.404

TG= triglyceride; HDL= high density lipoprotein; LDL= low density lipoprotein.

Table (8): Biomarkers, thyroid function and lipid profile of the diseased groups:

		Mild (A)	Moderate (B)	Severe (C)	P value		
		N=6	N=14	N=25			
Adiponectin	**Median IQR**	3252.5 (2765-3695)	1480 (641.3-3105)	980 (355-2627.5)	0.022*		
					I vs II	**I vs III**	**II vs III**
					0.048*	0.008*	0.299
Thioredoxin	**Median IQR**	287.5 (278.8-387.5)	365 (322.5-556.3)	440 (260-412.5)	0.097		
					I vs II	**I vs III**	**II vs III**
					0.106	0.652	0.051
TSH	**Median IQR**	0.9 (0.6-2.4)	2.8 (1-4.3)	1.7 (0.5-4.8)	0.536		
					I vs II	**I vs III**	**II vs III**
					0.248	0.689	0.429
Free T3	**Median IQR**	4 (3.8-6.3)	4 (3-5)	3 (2-3.5)	0.003*		
					I vs II	**I vs III**	**II vs III**
					0.578	0.006*	0.006*
Free T4	**Mean±SD**	15.1±3.4	16.7±1.9	13.5±2.6	0.002*		
					I vs II	**I vs III**	**II vs III**
					0.39	0.343	0.001*
TC	**Median IQR**	261 (236.5-366.5)	237 (162.5-311.8)	260 (201.5-328.5)	0.526		
					I vs II	**I vs III**	**II vs III**
					0.322	0.484	0.447
TG	**Median IQR**	177.5 (91.5-251)	99 (89.5-174.5)	130 (90-219.5)	0.497		
					I vs II	**I vs III**	**II vs III**
					0.248	0.484	0.473
HDL	**Mean±SD**	47.2±9.3	43.5±11.5	45.7±10.6	0.742		
					I vs II	**I vs III**	**II vs III**
					0.765	0.950	0.817
LDL	**Median IQR**	204 (144.5-236.8)	174.5 (110.8-223)	158 (119-213.5)	0.537		
					I vs II	**I vs III**	**II vs III**
					0.458	0.250	0.770

Discussion

OSA is a breathing disorder where episodes of apneas and hypopneas occur repeatedly lasting 10s or more during sleep [12]. PSG is considered the gold standard for diagnosing OSA.

However, PSG could not provide the bio-mechanics of the human UA, which may be used to identify the possible pathophysiology of OSA[13].

The present study included 90 subjects (45 patients with OSA, 23 control healthy obese and 22 control healthy non obese). We studied the metabolic disorders that affect OSA patients. This study was conducted on 90 subjects 45 control volunteers and 45 OSA patients (6 mild, 14 moderate, and 25 severe), their ages Mean±SD 57.2±8.9, 33.3% males, and 66.7% females, 24.4% current smoker, 8.9% ex-smoker, and 66.7% non-smoker.

In this study BMI showed a distinguished significant variation among studied groups (OSA patients, control obese and non-obese groups) with Mean±SD (44.4±6.5, 39.5±3.8, and 23.8±2, p=0.001 respectively). This in agreement with S. Alabaf et al.,[14]

who found that Approximately 30% of patients with a BMI greater than 30 and 50% of those

with a BMI greater than 40 have OSA. Neck circumference was increased in OSA patients than control obese and non-obese subjects with Mean ± SD (46.2±4.3, 36±2.7, 30.5±2.3, p= 0.001 respectively). This in agreement with Chai-Coetzer CL et al.,[15] who found that A large neck circumference has been associated with an increased risk of OSA. In addition, neck circumference of 40 cm or greater had a sensitivity of 61% and a specificity of 93% for OSA, regardless of the person's sex.

The prevalence of HTN in this study was more among OSA patients than control obese and non-obese subjects (57.8%, 17.4% and 0%, P= <0.001* respectively). This in agreement with Patel et al.,[16] who found that the prevalence of HTN in OSA patients was between 30% and 70%.

In our study DM was found in 20% of OSA patients. This in agreement with Yingjuan et al.,[17] who found that 30.1% of OSA patients had Type 2 DM.

In this study we found that PASP was significantly higher in patients with OSA than in control obese and non-obese subjects (57.1±12vs. 19±4.1vs. 19.8±3.3, P=<0.001* respectively).
This in agreement with Abou Shehata et al.,[18] studied 54 patients with OSA and reported increased PASP in 44.4% of the studied group, and Laks et al.,[19] reported pulmonary hyper-tension in 42% of OSA patients of his studied group.

TRX is one of the oxidative stress biomarkers. In our study there was significant increase in TRX level among OSA patients more than control obese and non-obese subjects with (P= 0.036*). This in agreement with Qian Guo et al.,[20]

who found that TRX level was significantly increased in OSA patients more than healthy group. However in contrast to our study they found that TRX level increased with the severity of OSA and it may be used as severity indicator of OSA. The absence of significant difference between mild, moderate and sever cases may be due to decrease the number included in our study

In our study we found that there was no significant difference in a diponectin among OSA patients and control group. This in disagreement with Mohamed et al.,[21]

who found lower serum adiponectin level among OSA patients than control group. This may be due to decrease number of the studied groups and that our control group included obese subjects.
However we found a significant decrease in serum a diponectin level with increased the severity of OSA patients (P= 0.022*). This in agreement with Mohamed et al.,[21] who found that serum adiponectin levels were significantly decreased with increased severity of OSA.

Conclusion

OSA is a serious condition that can be diagnosed with polysomnography and is associated with cardiovascular and metabolic comorbidities.

Acknowledgements
Authors would like to express their gratitude to all staff member in chest department and clinical pathology department for their great and valuable efforts.
Conflict of interest: The authors declare that they have no conflicts of interest relevant to this article.
Funding: There are no current external funding sources for this study.

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