Impact of Obstructive Sleep Apnea and Obesity on Hypoxia Inducible Factor 1-alpha Protein Level

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Abstract

Background: Obstructive sleep apnea (OSA) and obesity lead to a hypoxic state, increasing the hypoxia-inducible factor 1-alpha (HIF1-α) level to achieve cellular adaptation.

Objectives: To clarify the correlation between HIF 1-α level with both OSA severity and obesity.

Patients and methods: A case-control study was conducted on patients attending the sleep disorders unit at South Valley University Hospital from March 2022 to July 2023. 64 patients were diagnosed by a standard nocturnal polysomnography (PSG). A blood sample was taken to detect HIF 1-α level.

Results: Considering the HIF 1-α level, our study disclosed no significant difference between controls and OSA patients (P = 0.92), while there was a statistically considerable difference between different OSA groups (P = 0.001). Also, there are statistically significant positive correlations between HIF 1-α serum level with all of the following, AHI (r = 0.381, P = 0.008), the number of desaturation index (ODI) (r = 0.51, P < 0.001). and waist circumference (WC) (r = 0.291, P = 0.045).

Conclusion: OSA severity is associated with an increase in HIF-1α levels and neck and waist circumference reinforces the role of obesity and fat distribution in OSA pathophysiology.

Keywords: Hypoxia-inducible factor 1- alfa (HIF1-α); Obstructive sleep apnea (OSA); Obesity

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Introduction

Obesity is a significant modifiable risk factor suspected to cause Obstructive sleep apnea (OSA), with a clear correlation between increasing body mass index (BMI) values (especially if BMI > 30 kg/m^2) and elevated risk of OSA. As BMI increases, the likelihood of experiencing sleep disturbances, particularly OSA, increases. **(Gharib and Loza, 2020; Amiri, 2023).**

The development of chronic intermittent hypoxia due to OSA decreased O_2 at the tissue level, leading to the development of adaptive mechanisms including hypoxia-induced signalling (as hypoxia-inducible factors (HIFs), stress responses, endoplasmic reticulum (ER), autophagy by reactive oxygen species (ROS), and others. These adaptive mechanisms promote modifications in metabolism to match the oxygen availability **(Xie and Simon, 2017; Lee et al., 2020).**

During normoxia, hypoxia-inducible factor 1-alpha (HIF 1-α) proteins undergo hydroxylation and subsequent degeneration. After hydroxylation, HIF 1-α interacts with von Hippel-Lindau protein (pVHL) and then promotes ubiquitin-proteasome degradation of HIF-α. When hypoxia occurs, the enzymatic activity of prolyl hydroxylase domain proteins (PHD) is inhibited, which stops HIF-α hydroxylation and ubiquitin-mediated proteasome degradation. Afterwards, the HIF-α subunit interacts with HIF-1β to form a transcriptional complex dimerization that enters the nucleus and binds with hypoxia-responsive elements (HERs). This combination promotes the expression of several downstream genes to maintain cellular oxygen homeostasis **(Semenza, 2019; Luo et al., 2022).** Some studies record an elevation in HIF-α levels among OSA patients **(Gabryelska et al., 2020; Polat et al., 2023).**

A hypoxic cycle because OSA (generalized hypoxia) and obesity (localized tissue hypoxia) may augment the increase of HIF-1α. So, this study will investigate the impact of either OSA or obesity on the HIF-1α serum level.

Patients and methods

This case-control study was done on the suspected cases attending the Sleep Disorders Unit, chest department, at South Valley University Hospital during the period from March 2022 to July 2023.

We included all the cases aged 18 to 60, with various degrees of OSA, excluding subjects with a known history of HBV, HCV, cholecystitis, hypothyroidism, Wilson disease, systematic inflammatory diseases, any evidence of neoplastic disorder, vascular disturbance (such as stroke, coronary artery disease), alcoholism, with any other chronic chest diseases. Also, patients with central apnea, Cheyne stokes breathing or a baseline O_2 saturation of < 90% were excluded.

Methods

I. History and examination: full: Medical history was taken, clinical examination was done with special emphasis on the calculation of BMI, and measurement of neck circumference (NC) and waist circumference (WC).

II. Investigation:

A. **Polysomnography (PSG):** Standard overnight full PSG level 1 was performed according to the American Association of Sleep Medicine (AASM) using SOMNO screen ^{TM} plus EEG 10-20 (SOMNO medics-Germany) **(Berry et al., 2020),** including the following parameters: the Apnea Hypopnea Index (AHI), the Respiratory Distress Index (RDI), the Number of Desaturation Index (ODI), the baseline O_2 saturation during sleep, the number of desaturations below 90%, and the longest desaturation.

The AHI was determined by calculating the ratio of apnea events to the total hours of sleep. For adults, AHI values were classified as follows: Normal (if AHI < 5), mild apnea (if 5 ≤ AHI < 15), moderate apnea (if 15 ≤ AHI < 30)

and severe apnea (if AHI ≥ 30) **(Berry et al., 2020).**.

B. Laboratory assessment: About six millilitres of venous blood sample was taken. The sample was allowed to clot for fifteen minutes at 37° C. Later, we got the serum by centrifugation at 4000 rpm for 20 minutes. The level of HIF 1-α was assessed using Human hypoxia-inducible factor 1α, HIF-1α ELISA Kit, Cat no: BZEK1618, Chongqing Biospes Co., Ltd, China, this kit was based on standard sandwich enzyme-linked immune-sorbent assay technology. The purified anti- HIF-1α antibody was pre-coated onto 96-well plates. And the HRP conjugated anti-HIF-1α antibody was used as detection antibodies. The standards, test samples and HRP conjugated detection antibody were added to the wells subsequently, mixed and incubated, then, unbound conjugates were washed away with wash buffer. TMB substrates (A & B) were used to visualize HRP enzymatic reaction. TMB was catalysed by HRP to produce a blue colour product that changed into yellow after adding acidic stop solution. The density of yellow is proportional to the HIF-1α amount of sample captured in plate. Read the O.D. absorbance at 450nm in a microplate reader, and then the concentration of HIF-1α can be calculated, Sensitivity: 0.5 ng/L, Specificity: 99%, Detection limits: 5 ng/L - 80 ng/L, inter CV 8.7%; intra CV 6.9%.

Ethical code: Ethical approval was obtained from the Ethical Review Board, code SVU-MED-PHY003-2-22-2-328.

Statistical analysis

Data were analyzed using the Statistical Package for Social Science (SPSS) software program version 25 (SPSS Inc., Chicago, IL). Testing for normality was done using the Shapiro test and accordingly, parametric and non-parametric tests were selected to compare the groups. A comparison between the patients with and without OSA was done using a student t-test and Mann-Whitney U test. The chi-square test was used in the comparison between two groups with qualitative data. Additionally, a comparison between different degrees of OSA was done using the ANOVA test for parametric and Kruskal-Wallis for non-parametric data. Spearman rho test was used in the correlation analysis. Receiver operating characteristics (ROC) curve analysis was used to assess the accuracy of HIF-1α in discriminating severe OSA from non-severe OSA. Simple linear regression was used to evaluate the impact of AHI and ODI on HIF-1α, separately.

Results

This study included 64 subjects. Their median age is 40.5 (30-44.82), and their mean BMI is 38.63 (±10.35). They are 42 (66%) males and 22 (34%) females., according to AHI values, subjects were classified as follows: 16 controls (if AHI < 5) and 48 OSA patients (if AHI > 5); in turn, OSA patients were divided into different degrees: 10 patients with mild apnea (if 5 ≤ AHI < 15), 22 patients with moderate apnea (if 15 ≤ AHI < 30), and 16 patients with severe apnea (if AHI ≥ 30).

(Table.1) disclosed the demographic, PSG parameters and HIF-1α protein level of the study population**,** Where the comparison between 16 controls and 48 OSA patients exhibited no statistically significant variance in basic characteristics ($p > 0.05$), except for snoring ($p < 0.001$), which is higher in OSA patients. All PSG parameters showed a statistically significant variance between control vs OSA patients ($P < 0.01$) including Apnea Hypopnea Index (AHI) (3.05 vs. 19 /h), Number of Desaturation Index (ODI) (3.25 vs 25.65 /h), minimal SpO_2 % (90.5 vs. 82 %), and the percentage of time with $SpO_2 < 90\%$ (0 vs 2.8 sec). Additionally, the level of HIF-1α doesn't differ significantly between controls and OSA patients ($P = 0.92$), regardless of OSA grades of severity.

Table 1. The demographic, PSG parameters and HIF-1α protein level of the study population

Variables		Group		Test	P-Value
		OSA (N=48)	Non-OSA (N=16)		
Age		44.0 (30.0-59.0)	39.0 (29.25-43.75)	MWU	0.447
Hight(cm)		164.5 (159.0 - 169.25)	165.0(161.2 - 170.0)	MWU	0.669
Weight (kg)		103.5 (89.0 - 123.75)	95.5 (90.25 - 108.0)	MWU	0.480
BMI (Kg/m^2)		38.77 ± 10.72	38.23 ± 9.48	t-test	0.859
NC (cm)		43.04 ± 4.26	42.62 ± 2.09	t-test	0.709
WC (cm)		122.0 (103.7 -134.2)	110.5 (103.2-116.0)	MWU	0.180
Sex	**Male**	34 (71%)	8 (50%)	X^2	0.225
	Female	14 (29%)	8 (50%)		
DM		18 (37.5%)	2 (12.5%)	X^2	0.119
HTN		16 (33.3%)	4 (25%)	X^2	0.755
Snoring		44 (91.7 %)	4 (25%)	X^2	< 0.001
Smoking		8 (16.7 %)	2 (12.5 %)	X^2	0.276
Chest diseases		10 (20.8 %)	0 (0%)	X^2	0.112
AHI (/h)		19.0 (15.28-32.72)	3.05 (1.92-4.93)	MWU	< 0.001
RDI (/h)		21.9 (14.73-39.93)	3.45 (2.07-5.2)	MWU	< 0.001
ODI (/h)		25.65 (6.72-37.75)	3.25 (2.1-7.28)	MWU	< 0.001
Minimal SpO2%		82.0 (72.0-86.0)	90.5 (87.75-92.0)	MWU	< 0.001
Baseline awake O2 saturation %		94.46 ±1.71	95.31 ±1.08	t-test	0.066
SpO_2 time <90% (sec)		2.8 (0.3-10.72)	0.0 (0.0-0.38)	MWU	< 0.001
Longest desaturation (sec)		78.2 (58.32-105.35)	135.0 (51.75-155.9)	MWU	0.251
HIF-1α (ng/L)		4.93 (2.46 – 13.14)	5.45 (2.32 - 12.46)	MWU	0.920

OSA: Obstructive Sleep Apnea; BMI: Body Mass Index; NC: Neck Circumference; WC: Waist Circumference; DM: Diabetes Mellitus; HTN: hypertension; AHI: Apnea-Hypopnea Index; RDI: Respiratory Distress Index; ODI: Number of Desaturation Index; HIF 1-α: hypoxia-inducible factor 1-alpha.

Comparing OSA grades (mild, moderate, and severe), there is a statistically significant difference between moderate vs severe groups in the anthropometric measurements as BMI (P = 0.001), NC (P < 0.001), and WC (P < 0.001) and between mild vs severe groups as in NC (P = 0.037), and WC (P = 0.013).

HIF 1-α serum level exhibits a statistically significant difference (P < 0.01) between mild vs severe (P = 0.049) and mild vs moderate (P = 0.045). (**Table.2, Fig.1).**

Table 2. PSG parameters and HIF-1α level regarding OSA severity

Variables	OSA Degree			Test	P- Value
	Mild (N=10)	Moderate (N= 22)	Severe (N=16)		
Age	41.5 (30.25- 65.75)	34 (26-50.25)	50.5 (42.25-59)	Kruskal	0.158
BMI (Kg/m²)	39.63 ±13.72	34.29 ± 10.64	44.38 ± 5.01	ANOVA	0.013 $ 0.001
NC (cm)	42.5 ± 3.41	40.95 ±3.95	46.25 ± 3.26	ANOVA	< 0.001 # 0.037 $ < 0.001
WC (cm)	117.5 ±14.32	106 ± 25.57	134.75 ±8.54	ANOVA	< 0.001 # 0.013 $ < 0.001
AHI (/h)	8.85 (7.72-9.07)	17.4 (15.6-20.02)	47.5 (34.78-56.65)	Kruskal	< 0.001 * 0.01 # < 0.001 $ < 0.001
RDI (/h)	9.2 (8.85-11.3)	19.1 (17.08-23.38)	49.65 (39.33-56.88)	Kruskal	< 0.001 * 0.005 # < 0.001 $ < 0.001
ODI (/h)	5.8 (4.72-25.3)	25.95 (7.45-35.33)	45.85 (21.3-59.45)	Kruskal	0.007 # 0.001 $ 0.005
Minimal SpO2%	84.5 (70.25-88.75)	83.5 (82.0-86.0)	72.0 (69.25-81.0)	Kruskal	0.01 $ 0.001
Baseline O2 saturation%	94.0 (93.25-94.75)	95.5 (95.0-96.0)	93.5 (92.0-94.25)	Kruskal	0.004 $ 0.005
SpO2 time < 90% (sec)	0.35 (0.1-6.10)	1.05 (0.3-6.65)	15.85 (3.4-42.65)	Kruskal	0.008 # 0.009 $ 0.008
longest desaturation (sec)	126.1 (66.25-130.2)	73.45 (55.38-101.6)	74.0 (60.62-95.75)	Kruskal	0.113
HIF-1α (ng/L)	1.61 (0.74 - 3.53)	5.44 (2.25- 21.33)	10.21 (5.6- 17.11)	Kruskal	0.001 * 0.045 # 0.049

OSA: Obstructive Sleep Apnoea; BMI: Body Mass Index; NC: Neck Circumference; WC: Waist Circumference; DM: Diabetes Mellitus; HTN: hypertension; AHI: Apnea-Hypopnea Index; RDI: Respiratory Distress Index; ODI: Number of Desaturation Index; HIF 1-α: hypoxia-inducible factor 1-alpha; *Mild Vs Moderate; # Mild Vs Severe; $ Moderate Vs Severe.

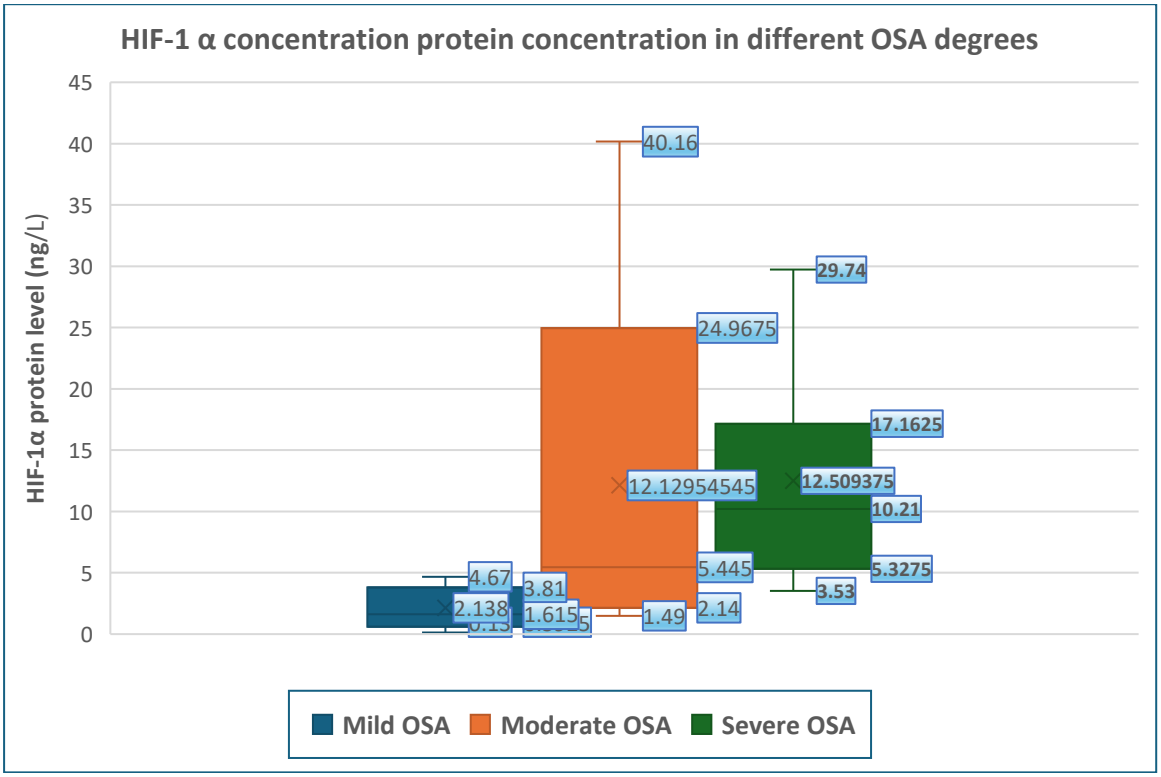

Fig.1. Box-blot showing HIF-1α protein concentration in different OSA degrees

Moderate positive correlations are noted between AHI and WC (r = 0.356, P = 0.013) and between AHI and NC (r = 0.36, P = 0.012). Additionally, moderate positive correlations are noted between ODI and WC (r = 0.43, P = 0.002) and between ODI and NC (r = 0.435, P = 0.002). Finally, moderate positive correlations are found between SPO2< 90 % time and WC (r = 0.306, P = 0.035), as shown in (**Table.3).**

Table 3. Spearman correlation between the severity of OSA and obesity

Variables		**AHI (/hr)**	**ODI (/hr)**	**SPO2< 90 % time (sec)**
BMI (Kg/m^2)	**Spearman r**	0.265	0.182	0.207
	p-value	0.069	0.216	0.158
WC (cm)	**Spearman r**	0.356	0.43	0.306
	p-value	0.013*	0.002*	0.035*
NC (cm)	**Spearman r**	0.36	0.435	0.275
	p-value	0.012*	0.002*	0.059

*: significant; BMI: Body Mass Index; WC: Waist Circumference; NC: Neck Circumference; AHI: Apnea-Hypopnea Index; ODI: Number of Desaturation Index.

Moderate positive correlations were disclosed between HIF-1α levels and with all the following, AHI (r = 0.381, P = 0.008), ODI (r = 0.51, P < 0.001), and RDI (r = 0.435, P = 0.002).

Also, weak positive correlations were noted between HIF-1α levels with WC (r = 0.291, P = 0.045), as shown in (**Table 4, Fig.2**)

Table 4. Correlation between level of HIF-1 α with BMI, WC and NC and PSG parameters in OSA patients.

HIF-1 α	BMI (Kg/m^2)	NC (cm)	WC (cm)	AHI (/hr)	ODI (/hr)	SPO_2 < 90 % time (sec)	RDI (/hr)	Minimal SpO_2%	Baseline awake O_2 saturation %	longest desaturation (sec)
R	0.242	0.177	0.291	0.515	0.493	0.167	0.435	-0.129	0.002	-0.003
p-value	0.097	0.229	0.045*	>0.001*	>0.001*	0.256	0.002*	0.381	0.989	0.984

*: significant; OSA: Obstructive Sleep Apnea; HIF 1-α: hypoxia-inducible factor 1-α; BMI: Body Mass Index; NC: Neck Circumference; WC: Waist Circumference; AHI: Apnea-Hypopnea Index; ODI: Number of Desaturation Index; RDI: Respiratory Distress Index.

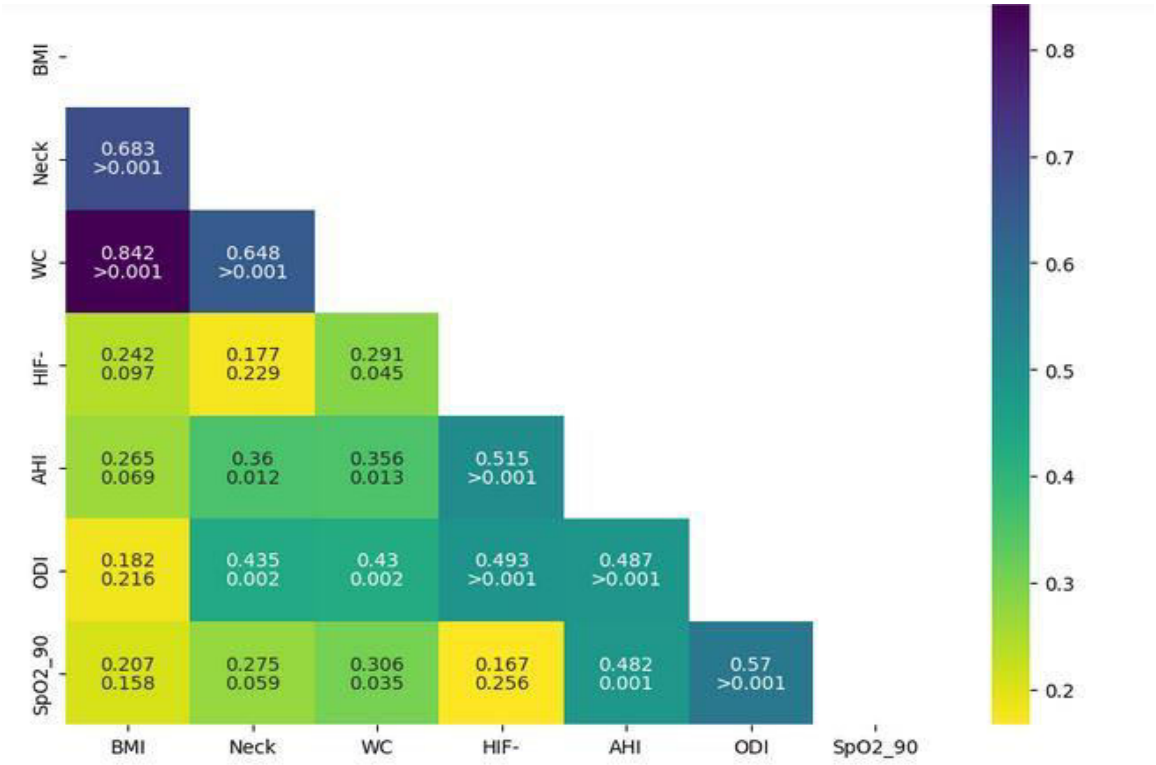

Fig.2. Heat map shows the correlation between the levels of HIF-1α, BMI, WC, and NC and PSG parameters in OSA patients.

The results of a simple linear regression analysis established that the main predictors for HIF-1α were AHI (p = 0.010, coefficient = 0.178) and ODI (p = 0.017, coefficient = 0.142), as shown in (**Table 5).**

Table 5. Simple linear regression analysis for predictors of HIF-1 α

Variables	Coefficient	95% CI		P-value
		lower	upper	
AHI (/hr)	**0.178**	**0.043**	**0.313**	**0.010**
ODI (/hr)	**0.142**	**0.026**	**0.258**	**0.017**

The optimal cut-off value was 4.60 ng/L, with a sensitivity of 87.50%, a specificity of 62.50%, PPV of 53.85%, NPV of 90.91%, and an overall accuracy of 70.83%. **(Fig.3).**

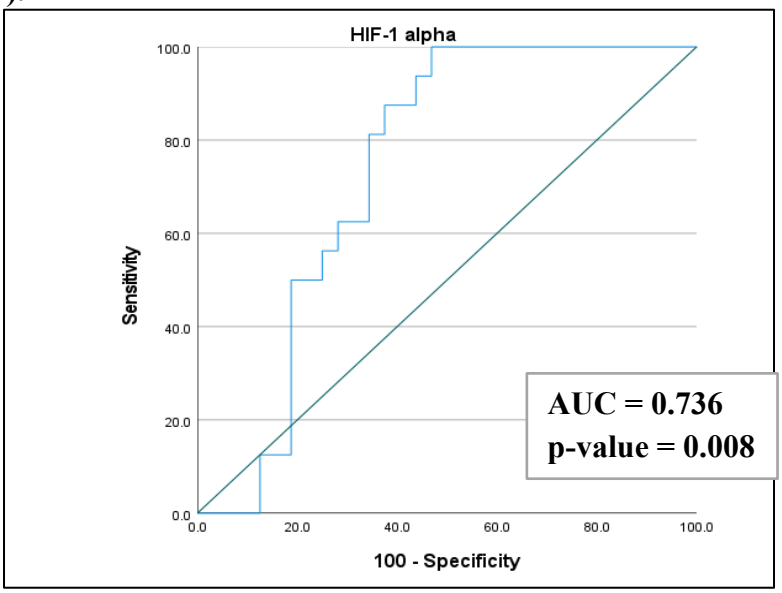

Fig.3. ROC curve of HIF-1α for diagnosis of severe OSA

Discussion

Obesity is one of the main risk factors for OSA, but recent studies suggest that OSA induces obesity or worsens it.

Our study explored a significant positive correlation between OSA severity (expressed by AHI and ODI) on one side and neck and waist circumference on the other side. This corroborates recent evidence that neck and waist circumferences are critical indicators of OSA severity. The fat accumulation of fatty tissue alerts the anatomical structure of peri-pharyngeal tissues and causes narrowing of the pharynx, highlighting local effects on airway patency **(Garzon et al., 2024).**

Also, increased abdominal fat elevates intra-abdominal pressure, reducing functional residual capacity (FRC) and forcing higher respiratory effort to overcome airway obstruction. As sleeping reduces neuromuscular activity, OSA patients suffer from poor sleep quality and interruption (OSA) **(Salzano et al., 2021; Zhang et al., 2024)**. These associations suggest that anthropometric measures are valuable for predicting OSA and guiding clinical management, particularly when PSG is unavailable.

Chronic intermittent hypoxia (CIH), characteristic of OSA, produces adipose tissue dysfunction and changes the metabolic process **(Chen et al., 2020).** Hypoxia induces more lipogenesis and hypertrophy in adipocytes, promoting the generation of a local hypoxic microenvironment,

which is termed "endogenous hypoxic." This can be explained by various mechanisms; one of them is the increased expression of HIFs **(Shao et al., 2021; Wang et al., 2022).**

Our study disclosed a moderate positive correlation between HIF 1-α level and OSA severity, assessed by AHI and ODI, which aligns with findings that HIF-1α expression increases with the frequency and duration of hypoxic episodes. Notably, significant elevations in HIF-1α were observed in moderate to severe OSA cases (AHI ≥ 15**) (Suen et al., 2019)**.

Additionally, a weak positive correlation was observed between waist circumference (WC) and level of HIF 1-α, suggesting that central adiposity contributes to adipose tissue hypoxia and subsequent HIF-1α expression. This can be explained by the fact that the hypertrophy of adipose tissue produces local tissue hypoxia, which increases the HIF-1α serum level **(Kang et al., 2023).**

However, the lack of significant difference in HIF 1-α level between controls and OSA patients can be explained by individual variations in fat distribution and metabolic activity even if they are matched in BMI. **Gabryelska and his colleagues (2020)** reported that there were other factors beyond overall adiposity, as the level of HIF-1α protein can increase owing to other causes like stimulation by insulin and interleukin-1 (IL-1) even under normoxic conditions.

Incorporating these insights in future research will provide a more illustration and comprehensive explanation of the complex mechanisms regulating HIF 1-α in OSA and highlight the multifactorial nature of its expression beyond adipose tissue hypoxia or hypoxic stimuli.

However, this study had some limitations, including the small number of patients, as we aimed to exclude any case with a possible factor that may cause hypoxia and disturb our results. Also, the small number of controls, as most of them refuse to continue PSG test and be included in our study. Larger studies with more cases are recommended for further investigation of our data

Conclusion

OSA severity is associated with a rise in HIF-1α level. Moreover, neck and waist circumference reinforces the role of obesity and fat distribution in OSA pathophysiology.

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