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Original Article

Association of dyslipidemia and hypoxemia in patients with obstructive sleep apnea hypopnea syndrome: a cross-sectional study

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Abstract: Objective: Studies have shown that dyslipidemia may contribute to chronic tissue hypoxia. However, it remains unclear whether dyslipidemia affects chronic hypoxia in patients with obstructive sleep apnea hypopnea syndrome (OSAHS). Therefore, from a clinical practice perspective, the purpose of this study was to investigate the effect of dyslipidemia on chronic hypoxia in OSAHS patients. Method: In athis cross-sectional survey, 320 consecutive OSAHS patients were enrolled. By screening under different conditions, 211 patients were finally enrolled in the study. Patients were grouped according to apnea-hypopnea index (AHI), into a mild-to-moderate (AHI < 30) group and severe OSAHS group (AHI ≥ 30). Results: Comparative analysis shows that 45% of mild-to-moderate OSAHS patients had severe hypoxemia. Univariate and multivariate regression analyses showed that AHI, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) had independent effects on *lowest oxygen saturation* ($LSpO_2$), and that AHI and TG levels had independent effects on *mean oxygen saturation* ($MSpO_2$). The patients were stratified by AHI and further grouped by TG and HDL-C abnormalities in each subgroup. A difference analysis showed that $LSpO_2$ and $MSpO_2$ were significantly decreased in OSAHS patients with dyslipidemia (high TG and low HDL-C levels) in the AHI ≥ 30 subgroup ($P < 0.05$). Finally, in order to further clarify the impact of the selected indicators of hypoxemia in OSAHS patients with different degrees of airway obstruction, subgroup analysis was conducted based on OSAHS severity. In the AHI < 30 subgroup, $LSpO_2$ was significantly decreased in patients with abnormal HDL-C. Conclusion: The results of this study indicate that abnormalities in TG and HDL-C, in addition to upper airway obstruction, are among the factors that aggravate chronic hypoxia in tissues from OSAHS patients.

Keywords: Obstructive sleep apnea hypopnea syndrome, dyslipidemia, hypoxemia, cross-sectional study

Introduction

In the field of obstructive sleep apnea hypopnea syndrome (OSAHS), previous studies focused on the related effects of hypoxia on blood lipids and considered chronic intermittent hypoxia as an independent risk factor for dyslipidemia [1-6]. However, no study has focused on whether dyslipidemia can aggravate chronic hypoxia in OSAHS patients. Recent basic research has shown that dyslipidemia diminished the oxygen conveying limit of red cells, accordingly causing tissue hypoxia [7-9]. Most studies generally believe that large airway obstruction is the main cause of hypoxemia in OSHAS patients. However, the current clinical evidence shows that it is still difficult to alleviate hypoxemia in some OSAHS patients with dyslipidemia after continuous positive airway pressure (CPAP) or surgical treatment to resolve upper airway obstruction [10-12]. At the same time, guidelines for the diagnosis and treatment of OSAHS also clearly point out that when evaluating therapeutic effect, close attention should be paid to the changes of hypoxemia in patients along with the improvement of apnea-hypopnea index (AHI) [13, 14]. The above clues suggest that it is necessary to further study

whether dyslipidemia, in addition to upper airway obstruction, can aggravate chronic hypoxia in OSAHS patients.

In recent years, much research has paid attention to OSAHS. For example, recent studies have shown that dyslipidemia can change the erythrocyte membrane structure and deformability by affecting the Na^+ K^+-ATP enzyme signal transduction pathway, thereby reducing its oxygen carrying capacity and ultimately leading to chronic hypoxia in tissues [8, 15]. Other studies have found that abnormal lipid metabolism in the body in patients with metabolic syndrome can reduce the filterability of red blood cells, thereby aggravating hypoxia in the body [7, 16, 17]. The above evidence further suggests that tissue hypoxia in some OSAHS patients may be due to airway obstruction, and dyslipidemia may also be an important factor in aggravating tissue hypoxia. Therefore, further evidence is needed to verify the possibility of this problem and to provide sufficient evidence for guiding diagnosis and treatment in the future.

Therefore, in this study, from the perspective of evidence-based medicine, we collected blood biochemical indexes and polysomnography (PSG)-related values related to metabolism, such as blood lipids and blood glucose, of patients with OSAHS admitted to our hospital. Through univariate and multivariate regression analysis, we found that there was an independent influence of tissue hypoxia in OSAHS patients on the blood biochemical indexes. A subgroup analysis was carried out according to AHI to further explore the influence of dyslipidemia on hypoxia-related values of OSAHS patients in order to provide evidence-based medicine for improving the influence of dyslipidemia on chronic hypoxia in this population.

Methods

Study population

A cross-sectional study was performed by enrolling OSAHS patients who were hospitalized in the otolaryngology unit of the First Hospital of Hebei Medical University, China, between November 2016 to July 2021.

Patients were included if they met all the criteria as follows: 1) Adult patients (age > 18 years); 2) Clinically, they had typical nocturnal sleep snoring with apnea and daytime sleepiness (Epworth sleepiness scale score ≥ 9); 3) The examination revealed narrowing and obstruction of any part of the upper airway, recurrent episodes of apnea and hypopnea > 30 times per night during 7 h of sleep or a sleep apnea hypopnea index (AHI) ≥ 5 times/h. Patients were excluded if they met any of these criteria: 1) They had chronic obstructive pulmonary diseases, such as pulmonary arterial hypertension, or bronchial asthma, or other related sleep disorders including upper airway resistance syndrome, restless legs syndrome, or narcolepsy, that was found before presentation or during hospitalization; 2) They had cardiac, or respiratory failure and chronic kidney related disease, or other systemic diseases; 3) They had taken or were currently taking medications affecting sleep breathing and lipid-lowering medications for a short time before presentation; 4) They had an upper respiratory tract infection a short time before presentation; or 5) They had refused to sign the informed consent form.

Anthropometric and biochemical measurements

Baseline anthropometric indices were measured blindly by trained doctors. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2). Blood pressure was measured in a supine position using a mercury sphygmomanometer after a 10-min rest, and the mean of three measurements was recorded. All anthropometric measurements were performed based on a double-blind design. After fasting for at least 10 h, peripheral blood samples were drawn from the anterior elbow veins of all subjects in the morning after PSG monitoring, to determine the concentrations of fasting blood glucose (FBG) by an enzymatic colorimetric method based on activity of glucose oxidase enzyme. The serum concentrations of triglyceride (TG), total cholesterol (TC) and low-density lipoprotein (LDL) were evaluated by enzymatic method using an AU5800 autoanalyzer (Beckman Coulter Inc., CA, USA). The concentration of LDL cholesterol was calculated by the Friedewald's equation method.

Fasting blood samples were drawn from the anterior elbow veins of all subjects the morning after PSG monitoring. Blood lipid profile (TG, total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and HDL-C) and fasting blood glucose (FBG) were measured by routine procedures in the clinical laboratory of the hospital.

Polysomnography

A full-night polysomnography was performed during the subject's habitual sleep time [18, 19]. Sleep was monitored by electroencephalograms (EEG), including left and right electrooculograms (EOGs), submental electromyograms (EMG), nasal and oral airflow, snoring, electrocardiograms (ECGs), thoracic/abdominal movement, pulse oxygen saturation, and body position. Respiratory events were scored according to the criteria established by the American Academy of Sleep Medicine (AASM) [20]. Total sleep time was defined as the period from sleep onset to final awakening.

Primary outcome measures (lowest oxygen saturation ($LSpO_2$) and mean oxygen saturation ($MSpO_2$))

As described by Liu et al. [21], the peripheral SpO_2 signal was recorded as part of the overnight PSG test, with a pulse oximeter placed on the fingertip. The pulse oximeter was set to have an averaging time of 1 s and a sampling rate of 10 Hz. The $LSpO_2$ was defined as the lowest saturation reached during sleep, the $MSpO_2$ was defined as the mean saturation during sleep, and the time length of SpO_2 < 90% (TS90%) was measured in minutes, with saturation levels below 90% at nighttime. Data were acquired automatically with Sleepware software (Respironics Inc.) after being manual scored. Severe hypoxemia was defined as a nocturnal arterial lowest oxygen saturation $LSpO_2$ < 80%.

Statistical analysis

Data were presented as means ± standard deviation (SD). Differences between two groups were analyzed using Student's t-test; non-normally distributed data wre presented as medians (interquartile range), and the differences between groups were assessed using the Mann-Whitney U test. The measured data were analyzed by analysis of variance, and the comparison among groups of enumerated data was tested by chi-square test. In the correlation analysis, Pearson analysis was used for a normal distribution, and Spearman analysis was used for a non-normal distribution. A multiple linear regression model was established to analyze the influencing factors of dyslipidemia on PSG hypoxia values of OSAHS patients. We further performed subgroup analysis, and according to AHI, OSAHS patients were divided into a mild-to-moderate group or a severe group (AHI < 30 times/h was defined as mild to moderate, AHI > 30 times/h was severe). All statistical analyses were performed using SPSS software, version 21.0 (IBM, Armonk, USA). P < 0.05 was considered significant.

Results

Basic characteristics of the study subjects

A total of 320 OSAHS hospitalized patients were selected in the study by continuous grouping. Then, 109 patients were excluded, including 29 patients with chronic obstructive pulmonary disease, bronchial asthma, other pulmonary diseases, and other sleep disorders, 42 patients who had taken or were taking sleep-affecting respiratory drugs and lipid-lowering drugs for a short time before treatment, 13 patients who had an upper respiratory tract infection before treatment, and 25 patients who had refused to join the group or sign the informed consent. Finally, a total of 211 OSAHS patients were included in the final study.

OSAHS patients were divided into a mild-to-moderate group (AHI < 30) or severe group (AHI ≥ 30) according to the AHI, an index reflecting the degree of upper airway obstruction. The sleep status and PSG values of OSAHS patients were analyzed. The results show that there were significant differences in metabolism-related indexes such as blood lipid, blood glucose, blood pressure, obesity degree, and nighttime sleep and hypoxia-related values between the two groups (all P < 0.05). It was also found that even when AHI was mild to moderate (AHI < 30), 45% of patients still had severe hypoxemia (**Table 1**). This result indicates that there may be other factors besides atmospheric duct obstruction affecting chronic hypoxia in OSAHS patients.

Univariate regression analysis of hypoxia-related values for PSG in OSAHS patients

$LSpO_2$ and $MSpO_2$ were used as outcome indicators, and metabolic-related indicators that may affect hypoxia in OSAHS patients were used as influencing factors. Univariate regression analysis was performed. The results show that TG, HDL-C as biochemical indicators, BMI and WC as general characteristic values, and NREM and average heart rate as PSG values have significant effects on hypoxemia in patients with OSAHS (all P < 0.05, **Table 2**).

Table 1. Basic characteristics of the study subjects

		All patients	AHI < 30	AHI ≥ 30	t/χ^2	*p* value
No. patients		211	40	171	-	-
General characteristics	Gender, male n (%)	18 (86.70%)	31 (80%)	152 (88%)	1.850	0.154
	BMI	30.1 (5.80)	26.6 (5.34)	30.45 (4.95)	-3.843	**0.010**
	Smoking n (%)	70 (33.15%)	13 (32.5%)	57 (33.3%)	0.088	0.487
	Alcohol consumption n (%)	79 (27.40%)	13 (32.5%)	66 (38.5%)	0.555	0.311
Metabolic-related indexes	TC (mmol/L)	4.9 (0.99)	5.13 (2.14)	4.89 (0.94)	-0.610	0.542
	TG (mmol/L)	1.92 (1.48)	1.21 (1.15)	1.91 (1.44)	-1.840	**0.042**
	HDL-C (mmol/L)	0.98 ± 0.19	1.04 ± 0.23	0.96 ± 0.19	1.833	**0.036**
	LDL-C (mmol/L)	3.34 ± 1.67	3.43 ± 0.77	3.32 ± 0.67	0.710	0.418
	FPG (mmol/L)	5.08 (1.04)	4.97 (0.38)	5.23 (1.26)		**0.045**
	SBP (mmHg)	137.3 ± 16.37	129.43 ± 14.47	139.23 ± 16.31	-2.648	**0.009**
	DBP (mmHg)	88.52 ± 12.95	83.96 ± 10.21	89.59 ± 13.33	-1.897	**0.006**
PSG-related parameters	AHI (events/hour)	57.7 (28.3)	22.21 (13.4)	62 (21.6)	-7.452	**< 0.001**
	NREM	79.771 (8.2)	76.116 (18.4)	80.621 (7.6)	-1.348	0.178
	REM	18.6 (9.2)	18 (15.1)	18.1 (7.2)	-0.098	0.922
	Respiratory arousal index (events/hour)	3 (4)	3 (4)	6 (4)	-3.466	**< 0.010**
	$LSpO_2$ (%)	64.254 ± 16.234	80.348 ± 5.581	60.515 ± 15.604	5.788	**< 0.001**
	$MSpO_2$ (%)	90.459 ± 3.984	94.303 ± 1.521	89.566 ± 3.847	5.591	**< 0.001**
	TS90%	30.8 (37.4)	38.5 (32.8)	39.69 (33.8)	-6.608	**< 0.001**
	Total number of respiratory events	435.5 (219.8)	171 (105)	475 (206)	-7.423	**< 0.001**
	Severe hypoxemia	185 (87.86%)	18 (45%)	167 (97.6%)	51.412	**0.001**

Significant *p* values ($P < 0.05$) are expressed in bold. Distributed data were presented as means ± standard deviation. Irregularly distributed data were presented as medians (interquartile range). Categorical data are presented as number of patients (%). BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHI, apnea-hypopnea index; $LSpO_2$, lowest pulse oxygen saturation; $MSpO_2$, mean oxygen saturation; TS90%, the time length of $SpO_2 < 90\%$; REM, rapid eyes movement; NREM, non rapid eye movement.

Multivariate regression analysis of hypoxia-related values for PSG in OSAHS patients

The above indicators with significant indigenous effects were incorporated into the multiple linear regression model to clarify the independent effect of each indicator on tissue hypoxia in OSAHS patients. The results show that TG, AHI, and HDL-C had significant effects on $LSpO_2$ (β = -5.38, 95% CI [-8.83 to -1.84]). (β = -0.22, 95% CI [-0.41 to -0.02]; β = 24.72, 95% CI [5.07 to 48.74]), and that AHI and TG had significant effects on $MSpO_2$ (β = -0.10, 95% CI [-0.14 to -0.06]; β = -0.69, 95% CI [1.37 to -0.05]). Therefore, we believe that TG and HDL-C have independent effects on tissue hypoxia in OSAHS patients. The higher the TG level or the lower the HDL-C level, the lower $LSpO_2$ and $MSpO_2$, and the more severe the hypoxia (**Table 3**).

Subgroup analysis of OSAHS population based on OSAHS severity

To eliminate the influence of this confounding factor of upper airway obstruction on tissue hypoxia and further reveal the effect of abnormal TG and HDL-C on tissue hypoxia in patients with OSAHS, the study still divided the population into severe AHI (AHI ≥ 30) or mild-to-moderate AHI (AHI < 30) subgroups. In each subgroup, TG and HDL-C abnormalities were grouped as exposure factors, and the differences in $LSpO_2$ and $MSpO_2$ between each group were analyzed. The results show that compared to normal TG and HDL-C groups in severe OSAHS patients, $LSpO_2$ and $MSpO_2$ were significantly decreased in patients with elevated TG and decreased HDL-C; similarly, in patients with mild-to-moderate AHI, $LSpO_2$ in patients with decreased HDL-C was significantly lower than that in the normal HDL-C group. The result further indicates that after excluding the hybrid effect of atmospheric duct obstruction, the abnormality of TC and HDL-C has a significant indigenous effect on chronic hypoxia of OSAHS patients (**Figure 1**).

Discussion

This study preliminarily showed that dyslipidemia, in addition to upper airway obstruction, could cause chronic hypoxia in OSAHS patients. First, we found that 45% of OSAHS patients

Table 2. Univariate regression analysis of $LSpO_2$ and $MSpO_2$ for PSG in OSAHS patients

	$LSpO_2$				$MSpO_2$			
	β	t	*p* value	95% CI	β	t	*p* value	95% CI
Age	-0.148	-0.999	0.320	-0.442 - 0.146	-0.026	-0.710	0.479	-0.98 - 0.046
Gender	5.390	1.241	0.217	-3.211 - 13.992	1.270	1.191	0.236	-0.842 - 3.382
BMI	-1.529	-4.910	**0.00**	-2.146 - -0.192	-0.383	-5.027	**0.001**	-0.533 - -0.232
AHI	-0.364	-6.166	**0.00**	-0.483 - -0.247	-0.125	-10.383	**0.001**	-0.149 - -0.101
NREM	-0.416	-2.442	**0.009**	-0.726 - -0.107	-0.153	-4.158	**0.001**	-0.227 - -0.808
REM	0.267	1.117	0.266	-0.206 - -0.740	0.150	2.610	**0.01**	0.036 - 0.263
average heart rate	-0.345	-2.072	**0.004**	-0.674 - 0.015	-0.118	-2.942	**0.004**	-0.117 - -0.039
TG	-1.848	-2.129	**0.035**	-3.566 - -0.129	0.482	-0.203	**0.027**	-0.907 - -0.057
HDL-C	14.17	1.92	0.05	-0.448 - 28.70	3.384	1.850	0.067	-0.238 - 7.707

Significant *p* values ($P < 0.05$) are expressed in bold. BMI, body mass index; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; AHI, apnea-hypopnea index; REM, rapid eyes movement; NREM, non rapid eye movement.

Table 3. Multivariate regression analysis of $LSpO_2$ and $MSpO_2$ for PSG in OSAHS patients

	$LSpO_2$			$MSpO_2$		
	β	95% CI	*p* value	β	95% CI	*p* value
AHI	-0.217	-0.411 - -0.023	**0.029**	-0.101	-0.137 - -0.064	**0.001**
TG	-5.381	-8.926 - -1.836	**0.004**	-0.685	-1.366 - -0.005	**0.048**
HDL-C	24.72	0.682 - 48.75	**0.044**	--	--	--

Significant *p* values ($P < 0.05$) are expressed in bold. TG, triglyceride; AHI, apnea-hypopnea index; HDL-C, high-density lipoprotein cholesterol.

with mild-to-moderate airway obstruction (AHI < 30) still had severe hypoxemia. The indexes that have a significant impact on hypoxemia in OSAHS patients were screened by univariate regression analysis, including AHI, TG, HDL-C, BMI, NREM and average heart rate. The conclusions of multiple regression analysis exhibited that TG and HDL-C were independent influencing factors causing a decrease of $LSpO_2$ and $MSpO_2$, in addition to AHI. The final subgroup analysis showed that in OSAHS patients with different degrees of airway obstruction, the abnormality of TG and HDL-C could significantly reduce the hypoxia saturation of OSAHS patients.

Previous clinical studies have indicated that patients with OSAHS are not expected to see improvements in their symptoms of hypoxia after airway obstruction is resolved [10, 11]. At the same time, some studies have found that statin therapy in OSAHS patients can alleviate the symptoms of vascular injury caused by chronic intermittent hypoxia [22]. This study for the first time revealed that dyslipidemia, in addition to airway obstruction, could affect tissue hypoxia in OSAHS patients. It provides a preliminary evidence-based medical study to explain the above research results.

At present, in the field of OSAHS research, most studies have focused on OSAHS as an independent risk factor for metabolic diseases such as dyslipidemia [23-26]. Dyslipidemia and redox imbalance are among potential mechanisms linking OSA with the development of vascular diseases [27]. However, few studies have focused on whether dyslipidemia aggravates chronic hypoxia in OSAHS patients from the opposite perspective. Studies have demonstrated that an increase of the erythrocyte membrane cholesterol concentration in patients with metabolic syndrome is related to the decrease of erythrocyte membrane fluidity and erythrocyte deformability [7, 28-30], which may decrease the oxygen-conveying capacity of red cells and put the body in a condition of chronic hypoxia [9, 31]. Recent studies have shown that hypercholesterolemia can increase the cholesterol content of the erythrocyte membrane [32, 33] and reduce the transmembrane oxygen diffusion rate, resulting in tissue hypoxia in patients [7, 26, 34, 35]. The above studies may support a possible pathologic mechanism of dyslipidemia exacerbating tissue hypoxia. In line with our findings, clinical studies have shown that the decrease of HDL-C and the increase of TG reduce the fil-

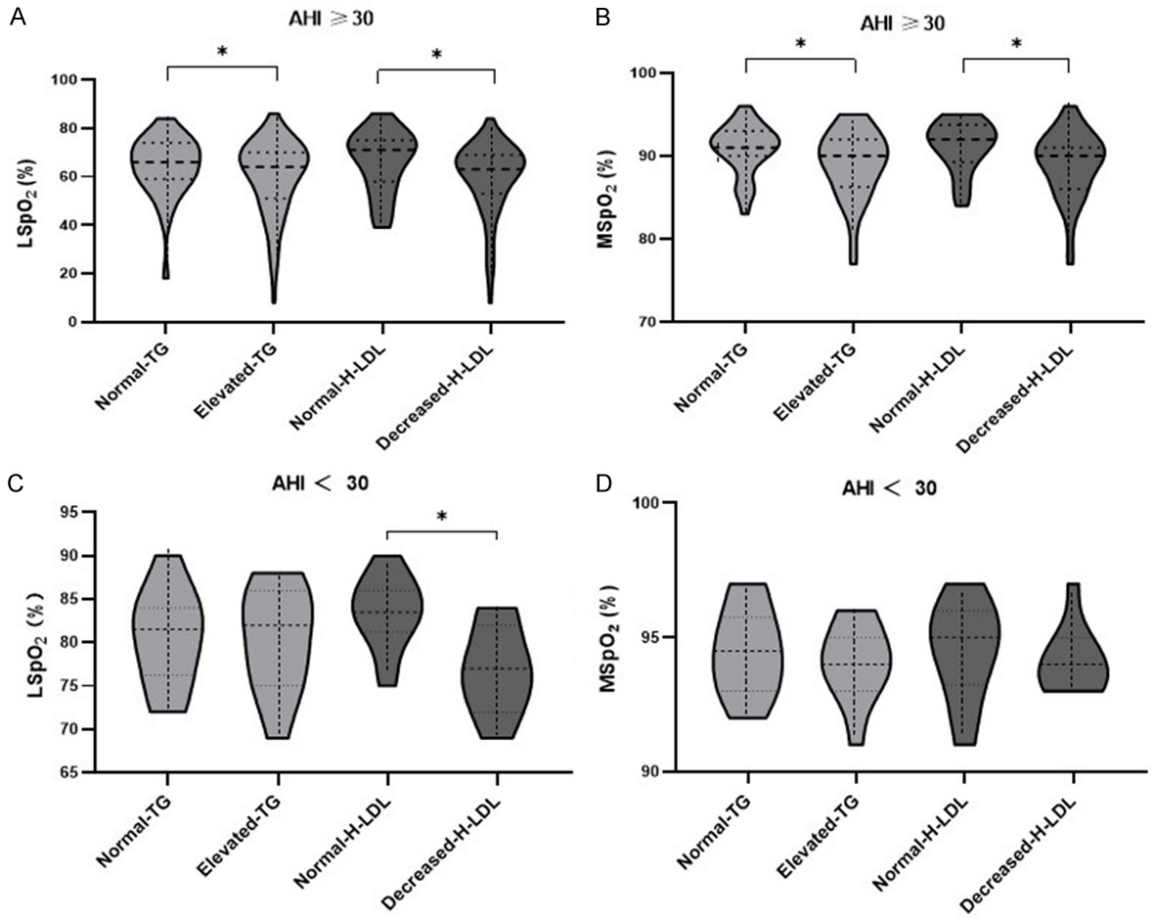

Figure 1. Violin plot result for subgroup analyses: (A) Differential comparison of $LSpO_2$ between the TG normal and abnormal groups and HDL-C normal and abnormal groups at AHI ≥ 30; (B) The difference in $MSpO_2$ between the TG normal and abnormal groups and the HDL-C normal and abnormal groups when AHI ≥ 30; (C) Differential comparison of $LSpO_2$ between the TG normal and abnormal groups and HDL-C normal and abnormal groups at AHI < 30; (D) Differences in $MSpO_2$ between the TG normal and abnormal groups and HDL-C normal and abnormal groups at AHI < 30. *P < 0.05. TG, triglyceride; AHI, apnea-hypopnea index; HDL-C, high-density lipoprotein cholesterol; $LSpO_2$, lowest pulse oxygen saturation; $MSpO_2$, mean oxygen saturation.

tration of red blood cells, leading to tissue hypoxia in patients. In this study, the effects of HDL-C and TG on hypoxia indexes $MSpO_2$ and $LSpO_2$ in OSAHS patients were clarified by single factor and multiple linear regression. The patients were partitioned into two subgroups as indicated by AHI, and the analysis of differences in each group showed that an abnormality of HDL-C and TG was one of the factors that aggravated hypoxia in the tissue of OSAHS patients, in addition to upper airway obstruction. Therefore, we believe that in OSAHS patients, besides the hypoxia caused by airway obstruction, a decrease of HDL-C and an increase of TG can also lead to tissue hypoxia by reducing the filtration of red blood cells.

There are some limitations in this study. First, it was designed as a cross-sectional study, and the establishment of causality was based on the reported results of basic and clinical research literature in the field of diseases such as metabolic syndrome [4, 11]. In the future, it is necessary to establish a prospective cohort and perform basic research on the OSAHS population to clarify the exact impact of dyslipidemia on tissue hypoxia in this population. Additionally, it should be noted that only a single-center sample data was collected in this study. In the future, multi-center large-sample verification is needed to establish the durability of the results.

Conclusion

Our research successfully showed that dyslipidemia, in addition to upper airway obstruction, was an independent influencing factor of tissue

hypoxia. Moreover, our data indicate that the degrees of plasma TG and HDL-C were substantially and independently related to the degree of hypoxia. The increase of TG or the decrease of HDL-C would aggravate the tissue hypoxia in OSAHS patients. Consistent with the conclusions from previous basic studies, our study shows that dyslipidemia can cause tissue hypoxia [1-6], which may also be one of the factors that aggravate chronic hypoxia in patients with OSAHS.

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Disclosure of conflict of interest

None.

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