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循环鞘氨醇-1-磷酸作为阻塞性睡眠呼吸暂停综合征诊断生物标志物的研究

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摘　要

目的：阻塞性睡眠呼吸暂停综合征(OSAS)是重大公共卫生问题，可增加患者代谢性疾病和心血管疾病的发病风险，本研究旨在明确OSAS发病及其严重程度与血清鞘氨醇-1磷酸(S1P)浓度的相关性。方法：纳入111名肥胖受试者，均接受夜间多导睡眠监测(PSG)评估肥胖手术适应症。其中有86例确诊为OSAS患者，25例则作为对照组。采用酶联免疫吸附试验(ELISA)检测血清S1P水平，收集并分析人口统计学及临床相关信息。结果：相较于对照组，OSAS患者的血清S1P水平显著降低；进一步分析可见，OSAS患者群体中，血清S1P水平随病情严重程度的加剧呈逐步下降趋势。线性回归分析结果证实，血清S1P水平与呼吸暂停低通气指数(AHI)存在显著强负相关，而与最低血氧饱和度($LSaO_2$)则呈明显正相关关系。受试者工作特征(ROC)曲线分析表明，血清S1P在OSAS筛查中的预测效能优于Epworth嗜睡量表(ESS)和STOP评分。结论：相较于对照组，OSAS患者血清S1P水平显著下调，且其水平高低与疾病严重程度呈负相关；同时血清S1P在OSAS诊断中具有良好的特异性、敏感性及阳性预测值，有望成为OSAS的潜在诊断性生物标志物。

关键词

阻塞性睡眠呼吸暂停综合征，鞘氨醇-1-磷酸，Epworth嗜睡量表

Circulating Sphingosine-1-Phosphate as a Diagnostic Biomarker for Obstructive Sleep Apnea Syndrome

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Abstract

Objective: Obstructive sleep apnea syndrome (OSAS) is a significant public health issue that increases patients' risk of developing metabolic and cardiovascular diseases. This study aims to clarify the association between OSAS incidence and severity with serum sphingosine-1-phosphate (S1P) concentrations. Methods: A total of 111 obese subjects were enrolled and underwent overnight polysomnography (PSG) to assess eligibility for bariatric surgery. Among them, 86 were diagnosed with OSAS, while 25 served as the control group. Serum S1P levels were measured using enzyme-linked immunosorbent assay (ELISA), and demographic and clinically relevant information was collected and analyzed. Results: Compared with the control group, serum S1P levels were significantly reduced in OSAS patients. Further analysis revealed that within the OSAS patient cohort, serum S1P levels exhibited a progressive decline with increasing disease severity. Linear regression analysis confirmed a significantly strong negative correlation between serum S1P levels and the apnea-hypopnea index (AHI), while a marked positive correlation was observed with the lowest arterial oxygen saturation ($LSaO_2$). Receiver operating characteristic (ROC) curve analysis indicated that serum S1P demonstrated superior predictive efficacy for OSAS screening compared to the Epworth Sleepiness Scale (ESS) and STOP score. Conclusion: Compared with the control group, serum S1P levels were significantly downregulated in OSAS patients, and their levels showed a negative correlation with disease severity. Simultaneously, serum S1P demonstrated good specificity, sensitivity, and positive predictive value in OSAS diagnosis, suggesting its potential as a diagnostic biomarker for OSAS.

Keywords

Obstructive Sleep Apnea Syndrome, Sphingosine-1-Phosphate, Epworth Sleepiness Scale

1. 引言

阻塞性睡眠呼吸暂停综合征(OSAS)是一项全球重大的公共卫生挑战，影响约 4%的普通人群和30%~50%的肥胖人群[1] [2]。OSAS 的特征在于间歇性缺氧和气流减少，这是由于睡眠期间上气道反复阻塞所致[3] [4]。OSAS 的诊断和严重程度分类通过夜间多导睡眠图(PSG)测量的呼吸暂停低通气指数(AHI)和最低血氧饱和度($LSaO_2$)进行验证[5]。大量证据表明，OSAS 患者发生高血压、脑卒中、糖尿病和代谢综合征等代谢性和心血管疾病的风险更大，且 OSAS 的严重程度与这些疾病的发病率和死亡率相关[6] [7]。鞘氨醇-1-磷酸(S1P)是一种多效的脂质信号分子[8]，它通过激活一个由 5 个 G 蛋白偶联受体组成的家族来发挥其生物学功能(S1PR1~S1PR5) [8] [9]。通过与不同的受体亚型结合，S1P 参与了几种生理和病理过程，包括炎症[8]、氧化应激[10]和血管内皮功能[11] [12]，它们都在 OSAS 的发病机制中起着至关重要的作用。基于此，我们提出推测，S1P 可能具备作为 OSAS 诊断与严重程度分级生物标志物的潜力。本研究以 OSAS 患者为研究对象，测定其血清 S1P 水平，探讨该指标与疾病严重程度的相关性，并初步评价其在 OSAS 诊断中的应用价值。

2. 资料与方法

2.1. 研究对象

本研究为前瞻性资料收集的回顾性分析研究，共纳入 111 例患者，纳入病例均为 2018 年 9 月至 2022 年 6 月在安徽医科大学第二医院普外科连续收治的患者。所有患者入院后均签署书面知情同意书，并配合完成空腹血样采集。研究所需的人口统计学信息及临床特征数据，均来源于医院电子病历系统的检索提取。本研究已获得安徽医科大学第二附属医院研究伦理委员会批准，批准文号为 YX2021-099(F1)。

2.1.1. 纳入标准

1) 通过多导睡眠监测方法，暂停低通气指数(AHI) ≥ 5 次的患者被诊断为 OSAS。2) 所有患者年龄均>18 岁。3) 患者临床资料完整。

2.1.2. 排除标准

1) 排除诊断有其他严重影响睡眠的相关患者，如不宁腿综合征、睡眠障碍等。2) 年龄小于 18 岁。3) 中枢性睡眠呼吸暂停每小时占 5 例以上。4) 总睡眠时间小于 5 h；5) 资料不全的患者。

3. 研究方法

3.1. PSG 监测

本研究所有受试者均通过多导睡眠图系统(Embla S4500, USA)开展多导睡眠图检测。根据美国睡眠医学学会(AASM) 2007 年标准方法对多导睡眠图记录进行分析与评分。呼吸暂停的诊断标准为气流减少程度 ≥90%，且持续时间达到或超过 10 秒；低通气需满足气流下降 ≥30%、持续 ≥10 秒，同时合并血氧饱和度下降 ≥ 4%这三项条件。AHI 是诊断和分级 OSAS 最常用的指标，定义为每小时睡眠中呼吸暂停和低通气事件的平均次数。AHI ≥ 5 的患者被诊断为 OSAS。根据 AHI 值，OSAS 患者可分为三组：轻度 OSAS (AHI ≥ 5 且<15)、中度 OSAS (AHI ≥ 15 且<30)和重度 OSAS (AHI ≥ 30)。将 AHI < 5 的人群纳入对照组。

3.2. 酶联免疫吸附试验(Enzyme-Linked Immunosorbent Assay, ELISA)

从受试者处采集血清样本，在 4℃条件下以 3000 转/分钟的速度离心处理。血清 S1P 浓度采用 ELISA 试剂盒定量检测。所有检测均严格遵循厂商操作规程进行。

4. 统计学方法

本研究统计学分析均借助 SPSS 18.0 软件完成；分类变量以例数或百分比形式呈现，组间比较则选用卡方检验或 Fisher 精确检验。连续数据以均数 ± SEM 或中位数(四分位数范围)表示，组间差异比较采用单因素方差分析，并通过 Tukey 事后检验开展组间两两比较。采用 Spearman 或 Pearson 相关分析，评估血清 S1P 水平与临床特征的相关性；运用线性回归分析，明确血清 S1P 与 AHI、$LSaO_2$ 的关联程度。以 $P < 0.05$ 作为差异具有统计学意义的标准。

5. 结果

5.1. 患者及对照者基本情况

本研究共纳入 86 例 OSAS 患者及 25 例健康对照者。两组人口统计学与临床基线资料见表 1。结果显示，OSAS 组与对照组在年龄、性别、体重指数(BMI)、收缩压及舒张压方面均未见显著差异。所有研究对象于入院时空腹采血，进行血常规及生化指标检测。分析发现，OSAS 患者的白细胞计数、血糖及尿

酸水平均显著高于对照组。两组受试者在红细胞计数、血小板计数、白蛋白、高密度脂蛋白、总胆固醇、甘油三酯、丙氨酸氨基转移酶、天冬氨酸氨基转移酶、尿素氮及肌酐等指标水平方面，均未显示出统计学差异。此外，OSAS 患者的 AHI 显著高于对照组，而 $LSaO_2$ 显著低于对照组。

Table 1. Comparison of demographic and clinical characteristics of OSAS group and control group
表 1. OSAS 组和对照组的人口统计学和临床信息对比

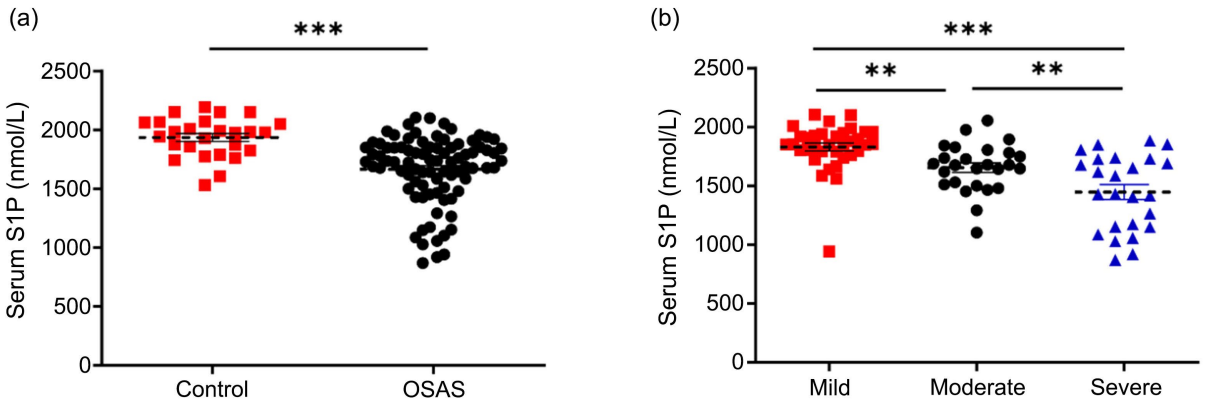
变量	OSAS (86)	Control (25)	P
年龄(岁)	33.22 ± 0.82	30.00 ± 1.5	0.06
男性(%)	40 (46.51)	6 (24.0)	0.06
身体质量指数	40.71 (35.14, 44.88)	39.03 (35.80, 43.18)	0.49
收缩压(mmHg)	135.70 (122.00, 146.0)	129.80 (124.80, 134.0)	0.22
舒张压(mmHg)	81.21 (73.00, 90.25)	78.09 (69.75, 87.00)	0.31
白细胞(10^9/L)	9.62 ± 0.33	8.2 ± 0.35	0.009
红细胞(10^{12}/L)	4.91 ± 0.08	4.81 ± 0.09	0.489
血小板(10^{12}/L)	288.0 ± 9.11	284.7 ±20.12	0.867
白蛋白(mg/L)	40.75 ± 0.525	41.73 ± 0.70	0.308
血糖(mmol/L)	5.90 (5.19, 6.63)	4.94 (4.64, 5.62)	0.009
高密度脂蛋白(mmol/L)	0.98 (0.83, 1.17)	1.07 (0.90, 1.23)	0.22
总胆固醇(mmol/L)	4.45 (3.92, 5.06)	4.29 (3.65, 4.83)	0.53
甘油三酯(mmol/L)	2.36 ± 0.36	1.75 ± 0.45	0.35
谷丙转氨酶(U/L)	45.79 ± 4.80	42.45 ± 8.80	0.73
谷草转氨酶(U/L)	30.85 ± 2.99	27.60 ± 3.82	0.55
尿素氮(mmol/L)	5.05 ± 0.19	5.12 ± 0.35	0.86
肌酐(mmol/L)	54.10 ± 1.34	52.75 ± 2.69	0.62
尿酸(mmol/L)	444.9 ± 11.20	391.4 ± 21.39	0.02
AHI	24.15 (8.60, 33.73)	1.36 (0.15, 2.3)	<0.0001
$LSaO_2$ (%)	71.16 (62.50, 81.25)	81.63 (74.00, 88.75)	0.0004

5.2. OSAS 患者与健康对照组血清 S1P 水平的比较分析

健康对照组的血清 S1P 水平显著高于 OSAS 患者(图 1(a))。进一步分析发现，在 OSAS 患者内部，血清 S1P 水平随疾病严重程度的加剧呈现进行性降低特征。如图 1(b)所示，轻度 OSAS 组患者的血清 S1P 水平明显高于中度及重度 OSAS 组。

5.3. 血清 S1P 水平 PSG 参数的关系

通过线性回归分析探讨了 OSAS 患者血清 S1P 水平与 AHI 及 $LSaO_2$ 的关联性。如表 2 所示，单变量线性回归分析显示，血清 S1P 水平与 AHI 呈显著负相关(β = −0.58 6, 95% CI: −9.496, −5.112)，与 $LSaO_2$ 呈显著正相关(β = 0.553, 95% CI: 0.377, 0.878)。多变量线性回归分析显示，血清 S1P 水平与 AHI 呈显著负相关(β = −0.380, 95% CI: −7.395, −2.071)，与 $LSaO_2$ 呈显著正相关(β = 0.272, 95% CI: 1.148, 9.733)。



注：(a) OSAS 患者与对照组血清 S1P 水平；(b) 不同病情严重程度 OSAS 患者血清 S1P 水平。所有数据采用均值 ± 标准差形式呈现；$^{**}P < 0.01$，$^{***}P < 0.001$。

Figure 1. S1P levels in OSAS patients and control group
图 1. OSAS 患者与对照组的 S1P 水平

Table 2. Correlation between serum S1P levels and PSG parameters
表 2. 血清 S1P 水平与 PSG 的相关性

Variables	Univariable (β, 95% CI)	*P*	Multivariable (β, 95% CI)*	*P*
AHI	−0.586 (−9.496, −5.112)	<0.001	−0.380 (−7.395, −2.071)	0.001
$LSaO_2$ (%)	0.553 (7.439, 14.664)	<0.001	0.272 (1.148, 9.733)	0.014

注：*为调整了性别、年龄、白细胞、血糖尿酸等因素。

5.4. 血清 S1P 水平诊断性能的 ROC 曲线与截断值分析

为明确血清 S1P 水平对 OSAS 的诊断价值，本研究进一步绘制受试者工作特征(ROC)曲线，并计算曲线下面积(AUC)以评估其诊断效能。如图 2 所示，血清 S1P 诊断 OSAS 的 AUC 为 0.808 (95% CI: 0.722~0.894)，确定最佳截断值为 1856.00 nmol/L，此时诊断灵敏度为 73.08%，特异性为 77.91%。作为临床常用的OSAS筛查工具，埃普沃思嗜睡量表(ESS)与STOP评分的AUC分别为0.697 (95% CI: 0.585~0.810)和 0.706 (95% CI: 0.599~0.811)。

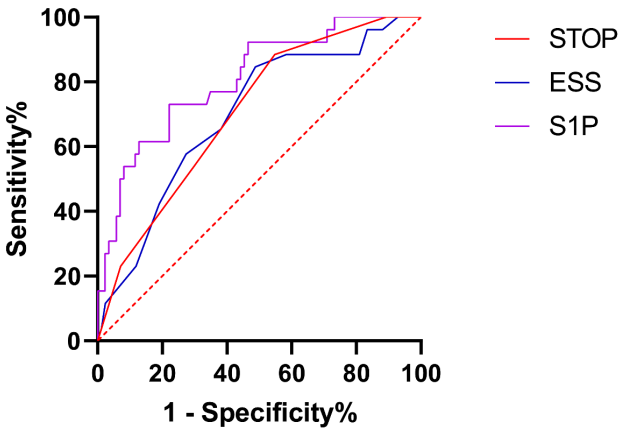


Figure 2. Receiver Operating Characteristic (ROC) curves of different predictive indicators for OSAS diagnosis
图 2. 不同预测指标在 OSAS 诊断中的受试者工作特征(ROC)曲线

6. 讨论

OSAS 是一种全球范围内日益严峻的公共卫生问题，其发病率和死亡率均较高，尤其在肥胖人群中更为突出。然而，由于多导睡眠监测(PSG)操作不便且普及性有限，多数 OSAS 患者未能获得及时诊断。本研究围绕 OSAS 患者血清 S1P 水平变化及与疾病严重程度的相关性展开分析，发现 OSAS 患者血清 S1P 水平显著下调，且其水平随病情进展呈持续下降趋势。这一结论表明，血清 S1P 具备作为 OSAS 潜在新型生物标志物的应用前景。

生物活性鞘脂在多种细胞过程中介导信号传导，对维持正常生理功能及疾病发生发展具有重要作用[13]-[16]。近年研究表明，该类鞘脂在急性肺损伤[17]、肺炎[18]及囊性纤维化[19]等疾病中，具有成为临床治疗靶点及诊断生物标志物的潜在价值。其中 S1P 作为一种重要的生物活性鞘脂，广泛参与多种细胞过程的调控。累积的临床证据进一步证实，S1P 在炎症相关疾病中发挥关键作用，例如高血压[20]、阿尔茨海默病(AD) [9]及脓毒性休克[21]等。先前研究表明，S1P 具备抑制炎症反应及强化内皮完整性的多重有益功效。一项针对 COVID-19 患者的研究显示，相较于健康对照者，COVID-19 患者的血清 S1P 水平显著降低，且其水平与 COVID-19 的疾病严重程度呈负相关[22]。Liu 等学者指出，血清 S1P 水平降低不仅能区分缺血性卒中、出血性卒中患者与健康人群，其水平还与缺血性卒中的病情严重程度相关[23]。因此，血清 S1P 可能成为炎症相关疾病的潜在生物标志物，并具有提示疾病严重程度的临床价值。

间歇性缺氧与氧化应激诱发的持续性低度全身炎症是 OSAS 患者的重要病理特征之一[2] [24] [25]。近期研究表明，OSAS 患者中存在的低度全身炎症状态，部分参与了 OSAS 相关代谢性疾病及心血管并发症的发生发展[25] [26]。多项研究表明，OSAS 患者循环中炎症介质，比如白细胞介素-6 (IL-6)、白细胞介素 1β (IL-1β)及肿瘤坏死因子-α (TNF-α)水平升高，且这些促炎介质与 OSAS 疾病严重程度呈正相关[27]-[29]。其中，S1P 作为一种重要的炎症介质，在中性粒细胞的活化与募集[30] [31]、B 细胞迁移[32]及淋巴细胞向循环中外渗[33]等过程中均发挥关键作用。S1P 水平降低可能与缺氧诱导的代谢紊乱直接相关：OSAS 患者反复间歇性缺氧可抑制鞘氨醇激酶 1/2 (SphK1/2)活性，减少 S1P 的合成；同时缺氧状态下，肝细胞及血管内皮细胞中 ApoM 表达下调，导致结合型 S1P 释放减少，循环中游离 S1P 水平下降。此外，OSAS 伴随的高尿酸、高血糖等代谢异常可通过氧化应激通路进一步抑制 SphK 活性，并促进 S1P 经磷酸酶降解。未来研究可补充检测 SphK1/2 活性及 ApoM、白蛋白水平，以明确缺氧环境下 S1P 合成–释放–降解的动态平衡变化；当前研究虽观察到 S1P 与 AHI 的负相关，但需辩证考虑缺氧可能通过下调 S1P 载体蛋白而非直接抑制合成通路导致其水平降低，这一机制有待进一步验证。多项研究表明，S1P 在炎症相关疾病中具有保护作用，提示其可能作为一种具有抗炎潜力的有益生物标志物。例如，Hsu 等人的研究表明，社区获得性肺炎患者血清 S1P 水平与病情严重程度呈负相关[34]。本研究检测了 OSAS 患者与健康对照组的血清 S1P 水平，结果显示，OSAS 患者血清 S1P 水平显著降低，且随着疾病严重程度加重而进一步下降。为深入阐明血清 S1P 与 OSAS 的关系，分析发现血清 S1P 水平与 AHI 呈负相关，与 $LSaO_2$ 呈正相关。通过 ROC 曲线评估并与 ESS、STOP 评分比较，血清 S1P 对 OSAS 表现出良好的预测效能，提示其在 OSAS 筛查中具有潜在应用价值，可作为反映 OSAS 发生及其严重程度的可靠生物标志物。

本研究存在若干局限性。首先，样本量相对较小，且所有受试者均来自同一医疗中心，未来需要更多中心、更大规模的人群研究以验证当前结果。其次，所有纳入研究的受试者均为肥胖患者，因此结论可能不适用于该特定人群之外的其他群体，有必要在正常 BMI 人群中开展进一步研究加以验证。此外，本研究虽然观察到 OSAS 患者血清 S1P 水平的变化，但其具体作用机制尚未明确，尚需通过后续体内外实验进一步阐明。

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