·综述·

阻塞性睡眠呼吸暂停综合征合并心血管疾病的血清预测指标

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【摘 要】 阻塞性睡眠呼吸暂停综合征(OSAS)以慢性间歇低氧为基础,通过多种发病机制导致心血管疾病(CVD)的发生。OSAS合并CVD已经成为威胁人类健康的重大疾病,引起了社会的广泛关注。既往研究主要集中在两者的病理生理机制上,而对血清学预测指标的研究较少。血脂指标简便易测、反应灵敏;脂肪因子指标可能是新的治疗靶点;蛋白质指标对调节糖脂代谢、早期诊断高血压以及心肌缺血起重要作用,本文将从上述3个方面进行重点阐述,以期为临床提供新的诊疗思路。

【关键词】 睡眠呼吸暂停,阻塞性;心血管疾病;预测指标
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Serological predictors of obstructive sleep apnea syndrome with comorbid cardiovascular disease

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【Abstract】 Obstructive sleep apnea syndrome (OSAS) is basically characterized by chronic intermittent hypoxia and leads to cardiovascular disease (CVD) through a variety of pathogeneses. OSAS with comorbid CVD has become a major disease threatening human health, arousing widespread concern in society. Previous studies mainly focused on the pathophysiological mechanisms of the two with few on serological predictors. Blood lipid is a sensitive index requiring simple and easy measurement; fat factor may serve as a new therapeutic target; protein indicators play an important role in glucose regulation and lipid metabolism, early diagnosis of hypertension and myocardial ischemia. Focusing on the above three aspects, this article aims to provide new insights into clinical diagnosis and treatment.

【Key words】 sleep apnea, obstructive; cardiovascular disease; predictors
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阻塞性睡眠呼吸暂停综合征(obstructive sleep apnea syndrome,OSAS)指每夜7 h睡眠过程中呼吸暂停及低通气反复发作30次以上,或睡眠呼吸暂停低通气指数(apnea hypopnea index,AHI)≥5次/h。OSAS基于慢性间歇低氧(chronic intermittent hypoxia,CIH),涉及炎症及内皮损伤、氧化应激、胸腔负压变化、自主神经功能紊乱、细胞凋亡、肾素-血管紧张素-醛固酮系统激活、血液高凝状态、内分泌及代谢异常等机制,引发冠心病、心房颤动、高血压、心力衰竭及心室重构[1]。因此,OSAS是心血管疾病(cardiovascular disease,CVD)发病和死亡的独立危险因素[2]。挖掘OSAS合并CVD病情的评估和预测指标,对于实现早期防治和精准治疗起关键作用。

临床实践中,血脂指标获得成本低、易获取、重复性好,对于预测OSAS合并CVD价值较高。各类蛋白质分子在调节机体糖脂代谢、早期诊断高血压和心肌缺血等方面对OSAS合并CVD起到关键性预测作用。

1 血脂指标

1.1 单核细胞/高密度脂蛋白胆固醇比值

单核细胞/高密度脂蛋白胆固醇比值(monocyte to high-density lipoprotein cholesterol ratio, MHR)是代表炎症及氧化应激的新颖指标。在CVD中,单核细胞粘附于内皮细胞表面并渗入至受损组织,诱导产生肿瘤坏死因子-α(tumor necrosis factor-α,

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TNF-α)、白细胞介素-1(interleukin-1,IL-1)和白细胞介素-6(interleukin-6,IL-6)等多种细胞因子。在此基础上,单核细胞进一步分化为巨噬细胞,吞噬氧化性低密度脂蛋白,形成泡沫细胞[3]。相反,高密度脂蛋白胆固醇(high-density lipoprotein cholesterol,HDL-C)可以逆转巨噬细胞的迁移,促进氧化胆固醇流出,同时抑制单核细胞的活化、粘附和增殖[3]。研究发现,MHR与AHI呈正相关,与最低血氧饱和度呈负相关,MHR可预测和识别OSAS合并CVD的严重程度[3,4]。从现有研究来看,MHR在OSAS合并CVD中的研究较少,未进行前瞻性随访及治疗前后的比较,血清单核细胞和HDL-C容易受饮食、药物、时间的影响,一次研究结果不能反映真实的趋势,应该多次测量不同时段的数据来反复验证。

1.2 ApoB/ApoAI比值

载脂蛋白B(apolipoprotein B,ApoB)是低密度脂蛋白的重要结构组成部分,而载脂蛋白AI(apolipoprotein AI,ApoAI)是HDL-C的主要结构成分,两者的比值可用于预测冠心病。据报道,OSAS患者ApoAI基因表达增加可能减少胰岛素抵抗[5],减少脂蛋白代谢异常,从而减少OSAS相关CVD事件[6]。研究发现,ApoB/ApoAI比值与OSAS患者AHI值呈正相关,该比值与单一ApoB、ApoAI相比,评估OSAS合并CVD风险的性能更强[6]。

1.3 血浆致动脉粥样硬化指数

血浆致动脉粥样硬化指数(atherogenic index of plasma,AIP)指甘油三酯与HDL-C的对数转换比率,已知AIP是冠心病的独立预测因子。研究发现,OSAS患者AIP升高,AIP与Epworth嗜睡量表(The Epworth Sleeping Scale,ESS)评分、AHI及氧减指数显著相关[7]。AIP与OSAS患者AHI独立相关,与病情严重程度呈正相关,CIH是诱发CVD的高危因素[8]。

2 脂肪因子指标

2.1 C1q/TNF相关蛋白-9

C1q/TNF相关蛋白-9(C1q/TNF-related protein-9,CTRP9)与脂联素高度同源,是一种新型心脏保护性心脏因子,起调节能量代谢和血管收缩、保护内皮细胞、抑制血小板活化和血管病理性重塑、稳定动脉粥样硬化斑块及保护心脏的作用。研究发现,CTRP9水平与AHI、氧减指数呈负相关,与左室射血分数呈正相关,证实了CTRP9与冠心病患者中重度OSAS的患病率独立相关[9]。一项研究发现microRNA-214-3p(miR-214-3p)的靶基因是CTRP9,并首次证明心肌梗死+CIH可上调miR-214-3p,抑制心脏CTRP9表达,加剧心室重塑,揭示CTRP9可能是一种新治疗靶点,用于治疗OSAS合并心肌梗死患者的病理性重塑[10]。

2.2 脂联素

脂联素(adiponectin,APN)是一种具有胰岛素增敏作用的强效抗炎脂肪因子。APN可能通过抑制线粒体融合和分裂的失衡而减轻CIH所致的胰岛损伤[11];激活环磷酸腺苷依赖的蛋白激酶(adenosine 5′-monophosphate-activated protein kinase,AMPK),和核因子κB(nuclear factor kappa-B,NF-κB)信号通路,对CIH诱导的成人心肌细胞损伤具有保护作用[12];APN促进胆固醇外流和逆向转运,促进HDL-C合成[13]。OSAS患者病情与APN水平降低和总胆固醇水平升高相关[13]。OSAS患者间歇低氧(intermittent hypoxia,IH)可通过抑制脂肪组织中APN mRNA水平分泌来降低APN水平[14],睡眠质量改善及血糖有效控制后APN水平升高[15]。因此,APN可作为OSAS合并CVD和高代谢风险评估的有益指标。

2.3 瘦素

瘦素是一种脂肪细胞衍生因子,作用于中枢黑皮质素原(proopiomelanocortin,POMC)-黑皮质素受体4(melanocortin-4 receptor,MC4R)通路和颈动脉体,促进呼吸改变和交感活动增加。IH增加瘦素释放和瘦素抵抗,直接刺激下丘脑-垂体-肾上腺轴,抑制胰岛素释放[16]。有研究表明,OSAS患者血清/血浆瘦素水平与AHI呈正相关[17]。因此,瘦素有望成为评估OSAS合并CVD的指标,用于预测OSAS合并CVD的发生,但未来仍需大样本数据研究支持。

2.4 摄食抑制因子-1

摄食抑制因子-1是一种调控食欲的脂肪因子,也是一种由心脏核结合蛋白-2编码的下丘脑肽,激活蛋白激酶B(protein kinase B,PKB)/细胞外调节蛋白激酶(extracellular signal-regulated kinase,ERK)途径抑制内质网应激,对抗心肌缺血/再灌注损伤而保护心脏[18]。研究证实,摄食抑制因子-1水平与冠心病的发病率和严重程度呈负相关[19],而OSAS患者摄食抑制因子-1水平与AHI呈显著负相关[20]。目前尚未有研究证实摄食抑制因子-1、OSAS、CVD三者之间的直接关系,未来还需大量的循证医学证据来证实。

2.5 网膜素-1

网膜素-1是一种抗炎脂肪因子,减少TNF-α

激活的巨噬细胞中促炎因子的产生。网膜素-1 通过抑制内质网应激和氧化应激,激活 AMPK/过氧化物酶增殖物激活受体(peroxisome proliferater-activated receptor, PPAR)δ 途径增加一氧化氮生成,防止高血糖诱导血管内皮功能障碍[21]。研究发现,网膜素-1 水平与 AHI 呈负相关,重度 OSAS 患者该水平显著降低,被认为是 OSAS 存在和严重程度的独立预测指标[22]。目前推断网膜素-1 可作为 OSAS 合并 CVD 的预测和评估指标,但是仍缺乏循证医学证据。

3 蛋白质指标

3.1 血管生成素样蛋白 8

血管生成素样蛋白 8(angiopoietin-like protein 8, ANGPTL8, or betatrophin)是一种主要由肝脏分泌,起调节脂肪酸、甘油三酯代谢的新型蛋白质,与冠心病的发生与发展密切相关。研究显示,血浆 ANGPTL8 水平与血脂(HDL-C 除外)、血糖水平呈正相关[23]。研究发现,通过下调 ANGPTL8 激活糖原合成酶激酶-3β(glycogen synthase kinase 3β, GSK-3β)/过氧化物酶体增殖物激活受体 γ 共激活因子-1(peroxisome proliferator-activated receptor γ coactivator-1, PGC-1α)信号通路,可增强胰岛素敏感性,并首次揭示了 ANGPTL8 与胰岛素抵抗指数呈正相关[24]。OSAS 患者 ANGPTL8 水平与 AHI 呈显著正相关[25]。总之 ANGPTL8 可通过调节糖脂代谢减轻心脏损害因素来延缓 OSAS 心血管损伤。

3.2 人软骨糖蛋白-39

人软骨糖蛋白-39(cartilage glycoprotein-39, YKL-40)在巨噬细胞、中性粒细胞、滑膜细胞、软骨细胞中分泌和表达,参与血管内皮损伤及修复、动脉粥样硬化。研究发现,OSAS 患者血清 YKL-40 水平增高可作为 OSAS 诊断的潜在指标[26]。OSAS 伴高血压患者 YKL-40 水平显著增高,并与 AHI 和最低血氧饱和度显著相关,因此其可能成为 OSAS 患者预防高血压的早期预警标志[27]。

3.3 缺血修饰白蛋白

缺血修饰白蛋白(ischemia-modified albumin, IMA)主要反映慢性炎症和氧化应激,有助于早期诊断心肌缺血。研究发现,OSAS 患者血清 IMA 水平显著增高,与 AHI 呈正相关[28,29],持续气道正压通气治疗后 OSAS 患者的 IMA 水平降低[29]。因此,血清 IMA 水平能揭示氧化应激、缺血和亚临床 CVD 风险,是检测 OSAS 合并 CVD 的良好指标[29]。

4 小 结

目前,OSAS 合并 CVD 是高度流行且严重威胁人类健康的公共卫生问题。探究灵敏度高、特异性好的血清学指标有利于早期评估和预测 OSAS 合并 CVD 的病情。但是目前的研究具有局限性:(1)临床研究样本量小,未进行大样本随机对照、治疗前后疗效对比、不同时段的测量结果比较,未来需要多中心、大样本的数据研究;(2)混杂因素较多,OSAS 和 CVD 存在共同的危险因素(如年龄、性别、肥胖等),需校正混杂因素对试验结果的干扰,将真实数据的趋势应用于临床实践中。

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