·综　述·

睡眠障碍与非酒精性脂肪性肝病

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[摘　要]　随着生活方式和膳食结构的改变,非酒精性脂肪性肝病(nonalcoholic fatty liver disease,NAFLD)的全球患病率逐年上升,给医疗卫生系统带来了沉重的负担。虽然临床医生对NAFLD病理生理机制的认识不断加深,但有效的治疗手段仍在探索中,生活方式干预仍是众多指南和医生推荐的NAFLD的一线疗法。睡眠是一个复杂的、高度调节的过程,对人类健康至关重要。众多研究表明睡眠障碍与慢性肝病尤其是NAFLD密切相关。然而,关于睡眠障碍如何影响NAFLD尚不明确。因此,本文旨在综述睡眠障碍与NAFLD之间的关系,使NAFLD患者从生活方式上进行改变,这将对NAFLD患者终身受益。

[关键词]　非酒精性脂肪性肝病;睡眠障碍;生活方式

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Sleep disorders and nonalcoholic fatty liver disease

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[**Abstract**]　With changes in life style and dietary structure, the global prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing year by year, posing a serious burden on health care systems. While clinicians' understanding of the pathophysiological mechanisms of NAFLD continues to improve, effective treatments are still being explored, and life style interventions remain the first-line therapy for NAFLD as recommended by numerous guidelines and physicians. Sleep is a complex, highly regulated process that is critical to human health. There is a growing consensus that sleep disorders are closely associated with chronic liver disease, especially NAFLD. However, it is not clear how sleep disorders affect NAFLD. Therefore, the purpose of this paper is to review the relationship between sleep disorders and NAFLD and to enable NAFLD patients to make life style changes, which will benefit NAFLD patients.

[**Key words**]　nonalcoholic fatty liver disease; sleep disorders; lifes tyle

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肝病在亚洲是一种高发疾病,近年来发展趋势已由传统的传染病向代谢紊乱转变[1]。非酒精性脂肪性肝病(nonalcoholic fatty liver disease,NAFLD)是一种多系统受累的疾病,其病理过程包括非酒精性肝脂肪变、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis,NASH)、NASH相关性肝硬化和肝细胞癌。一项Meta分析发现NAFLD全球患病率约为25%[2],而亚洲地区的NAFLD总患病率为29.62%,中国大陆的患病率为29.81%[3],更有学者预测中国在2030年NAFLD总数将达到3.148亿,是全球增长速度最快的国家[4]。睡眠占据我们人生1/3的时间,大量流行病学证据表明睡眠障碍与NAFLD密切相关。Miyake等[5]发现,睡眠时间短降低了日本中年男性NAFLD发病的风险。Okamura等[6]发现,睡眠时间≤5 h增加了NAFLD发病的风险。由此可见,睡眠与NAFLD之间的关系尚无明确定论。因此,充

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分了解睡眠障碍对NAFLD患者的影响，并给予NAFLD患者正确的睡眠建议，不仅可为临床医生治疗NAFLD等代谢性疾病开辟新思路和诊疗途径，同时也将使NAFLD患者最大化受益。

1　睡眠障碍与NAFLD机制相关

研究表明睡眠障碍与NAFLD之间存在双向关系，其相关机制可能与胰岛素抵抗、肥胖、肠道微生物和炎症相关。

1.1　睡眠障碍与胰岛素抵抗

研究表明睡眠障碍一方面减少大脑对葡萄糖消耗[7]，另一方面激活交感神经系统，导致交感-迷走神经失调，从而抑制胰腺β细胞分泌胰岛素[8]；同时，睡眠障碍导致血液中皮质醇升高，引起胰岛素抵抗及糖脂代谢紊乱[9]，而皮质醇的升高也可能促进脂肪组织的异位沉积，并加强游离脂肪酸向肝脏的过度输送，从而加重NAFLD[10]。

1.2　睡眠障碍与肥胖

研究表明睡眠质量差和睡眠时间短与肥胖相关，从而加重NAFLD。Benedict等[11]研究发现睡眠障碍导致的肥胖可能与前扣带皮层激活有关。前扣带皮层通过中轴皮层传递多巴胺，从而调节前扣带皮层回纹状体的谷氨酸含量，而纹状体在调节饥饿方面作用突出，从而增加进食量。另外，睡眠障碍通过增加胃泌素和下调瘦素水平，促进食欲，导致过量的能量摄入和脂肪异位沉积，从而增加患NAFLD的风险[12-13]。

1.3　睡眠障碍与肠道微生物

近期研究表明在长期昼夜颠倒的小鼠和时差紊乱的人群中，肠道微生物如放线菌减少50%，拟杆菌减少20%以及厚壁菌增加50%[14]。而肠道微生物失衡不仅通过“肠-脑轴”影响睡眠、情绪和认知功能，同时扰乱碳水化合物和脂质代谢，影响肝脏促炎与抗炎之间的平衡，从而加重NAFLD及发展到NASH[15]。而Jackson等[16]发现通过改善肠道微生物分布可延长睡眠时间并改善睡眠质量。然而也有研究发现短期睡眠障碍不会导致大鼠和人类主要微生物种群的改变[17]，这表明睡眠障碍引起的肠道微生物失衡可能受长期睡眠质量的影响。

1.4　睡眠障碍与炎症

肝脏持续的炎症反应是各种肝脏疾病中肝损伤和纤维化的关键触发因素。其中，参与NAFLD发病机制的至关重要的促炎因子如白细胞介素-6和肿瘤坏死因子-α已被证明与睡眠障碍密切相关[18-19]。这些细胞因子增加脂肪细胞脂肪分解产生游离脂肪酸，而肝脏游离脂肪酸增加导致胰岛素抵抗和氧化应激，从而进一步加重NAFLD。由此，发现睡眠障碍与促炎细胞因子存在联系，这也为临床医生诊疗炎症性疾病提供了新思路。然而，上述实验均属于小样本研究，因此，需多中心、大样本的大型临床队列研究和实验设计来进一步明确睡眠因素是否是炎症性疾病的危险因素及其生物学机制。

2　常见睡眠障碍类型与NAFLD

睡眠障碍包括失眠、睡眠相关呼吸障碍、昼夜节律障碍、异态睡眠、睡眠相关运动障碍和其他睡眠障碍等。众多研究表明NAFLD患者中最常见的睡眠障碍依次为阻塞性睡眠呼吸暂停(obstructive sleep apnea，OSA)、失眠和不宁腿综合征[20-21]。

2.1　OSA

OSA是与NAFLD关系最为密切的睡眠障碍类型。OSA是以睡眠期间上气道塌陷导致以慢性间歇性缺氧(chronic intermittent hypoxia，CIH)和打鼾为特征的代谢相关性疾病[22]。流行病学研究显示男性OSA患病率为10%~17%，女性为3%~9%[23]，而在NAFLD中发病率为64%~87%[24]。Chen等[25]发现NAFLD在轻度OSA患者中患病率为20.4%，而在重度OSA患者中高达52.1%。这表明NAFLD与OSA相互影响，研究表明CIH是连接OSA和NAFLD的重要因素。这可能是因为CIH通过上调缺氧诱导因子-1和参与脂肪生成的下游基因的表达，从而加剧肝脏氧化应激、活性氧产生和促炎因子释放，从而加重NAFLD并进展为NASH。同时，CIH与血脂异常、肝脂肪变性和胰岛素抵抗相关[26]。持续气道正压(continuous positive airway pressure，CPAP)是临床上治疗OSA的金标准。Chen等[27]发现，肝脏脂肪变性和血清转氨酶与OSA严重程度呈正比，并且在CPAP治疗3个月后ALT和AST水平显著降低。尽管众多研究发现CPAP可改善肝功能和血脂水平，但有研究表明CPAP治疗可能无法改善肝脂肪变性和肝纤维化[28-29]，然而这些结果都基于小样本实验，且CPAP治疗时间不超过1年。Shpirer等[30]发现为期2~3年的CPAP治疗改善了NAFLD患者肝脂肪变性。鉴于OSA参与NAFLD多种发病机制，临床对于OSA患者，即使BMI处于正常范围，也应进行腹部B超并进行相关肝功能和血脂检查，做到早发现、早诊断和早治疗；同时，对于无症状NAFLD患者也应进行OSA筛查；对于轻度NAFLD合并OSA患者，

还是以减重为主，暂不建议进行CPAP治疗[22]。

2.2　失眠

失眠是NAFLD患者的第二大睡眠障碍类型。这可能是因为肝脏在褪黑素代谢中起重要作用。肝功能受损患者日间褪黑素升高，引起昼夜节律紊乱，导致入睡困难和睡眠质量差[31]。此外，研究表明慢性肝病患者较正常人表现出更高的近端体温和较低的远端-近端皮肤温度梯度值[32]，这可能是由于慢性肝病患者高动力循环和皮肤血管扩张引起的核心体温调节受到影响，从而导致睡眠障碍[33]。匹兹堡睡眠质量指数（Pittsburgh sleep quality index，PSQI）是最常用的评估睡眠质量的量表，总分≥5分表明睡眠质量差，其敏感性为89.6%，特异性为86.5%[34]。众多研究表明NAFLD患者PSQI评分＞5分，这表明NAFLD患者入睡困难，睡眠持续时间短和睡眠质量较差[35-36]；同时睡眠质量差（PSQI＞5分）与高脂肪变性和高纤维化风险密切相关[37]。然而，一项对于中年韩国人的大规模队列研究表明睡眠质量在男性和女性患NAFLD风险方面无显著关联[38]。目前睡眠质量与NAFLD风险的研究相对较少，且多数为中年人，研究结论可能无法适用于儿童及青少年患者。鉴于NAFLD趋于年轻化，因此，今后应加强针对儿童和青少年的前瞻性、多中心和大样本量的随机高质量的临床试验。

2.3　不宁腿综合征

不宁腿综合征是指在夜间以难以抑制的移动四肢的冲动为特征的中枢神经系统感觉运动障碍性疾病，一般运动后可缓解。一项Meta分析表明，在所有类型的慢性肝病患者中，不宁腿综合征患病率为56%[39]。然而，目前关于不宁腿综合征与NAFLD发病机制的研究甚少，且美国和欧洲人群发病率高于亚洲人群。因此，关于亚洲NAFLD患者发生不宁腿综合征的发病率尚需进一步研究。

3　睡眠时间与NAFLD

美国睡眠医学学会和睡眠研究学会推荐的成人睡眠持续时间为7~9 h，老年人为7~8 h[40]。一项纳入2 172例日本人的研究发现，NAFLD患病率随着男性睡眠时间的增加而下降，女性在睡眠时间≤6 h及＞8 h组中NAFLD患病率最高[41]，而针对中国人的研究表明夜间睡眠时间＜6 h或＞8 h是NAFLD的独立危险因素[42-43]。一项针对韩国成年人的队列研究表明睡眠时间＞8 h与NAFLD发病率增加有关[44]。此外，午睡是国人独有的习惯，Hong等[45]发现白天午睡时间≥60 min增加NAFLD发病的风险。由此，睡眠时间多长对NAFLD患者最有益，与种族、性别和不同年龄段密切相关，尚未有统一定论。然而，根据目前的研究，我们能发现在中国睡眠时间＜6 h或＞8 h可能增加患NAFLD的风险。

4　总结和展望

由此可见，睡眠障碍在NAFLD患者中并不少见。睡眠障碍不仅是NAFLD的临床表现，也是NAFLD发生和发展的重要危险因素之一。因此，临床医生对NAFLD患者进行睡眠评估可能对疾病预后、转归和治疗有重大意义。多项研究表明6~8 h可能是NAFLD患者的最佳睡眠时间，这也可能是除饮食和运动外治疗NAFLD的一种新型生活方式干预。然而，目前关于睡眠障碍与NAFLD的相关性研究大多数属于横断面研究，两者之间的因果关系难以区分。此外，目前瘦型NAFLD与睡眠障碍之间的关系仍值得商榷。因此，迫切需要进行多中心、大样本和精心设计的队列研究，以确定改善睡眠是否对NAFLD有益。

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