

非酒精性脂肪性肝病(NAFLD): 危险因素、发病机制和治疗综述

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摘要

非酒精性脂肪性肝病(Non-Alcoholic Fatty Liver Disease, NAFLD)是世界范围内最常见的慢性肝病, 其全球患病率估计高达35%, 已成为一个重大的公共卫生问题。NAFLD包括单纯性脂肪肝, 脂肪性肝炎(NASH), 以及潜在的肝硬化和肝癌。NAFLD与胰岛素抵抗、肥胖、肠道微生物失调和遗传危险因素密切相关。肥胖的流行和2型糖尿病患者的增多极大地促进了NAFLD负担的增加。NAFLD的发病机制、确定治疗靶点和推进药物开发方面取得了稳步进展, 但仍存在重大挑战, 尚未有药物被批准用于该疾病。一旦诊断确定, 减肥、饮食调整和治疗潜在代谢综合征仍然是治疗的主要内容。指南建议在特定患者中使用吡格列酮和维生素E。本文综述了NAFLD和NASH的发病机制及危险因素, 为治疗策略的发展和有用的诊断工具提供见解。

关键词

非酒精性脂肪性肝病, 危险因素, 发病机制, 体重管理, 药物治疗

Non-Alcoholic Fatty Liver Disease (NAFLD): A Review of Risk Factors, Pathogenesis, and Treatment

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Abstract

Non-alcoholic fatty liver disease (NAFLD) represents the most prevalent chronic liver disorder globally, with an estimated worldwide prevalence reaching 35%, emerging as a significant public health issue. The disease spectrum encompasses a continuum from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which may progress to advanced fibrosis, cirrhosis, and hepatocellular carcinoma. NAFLD pathogenesis is strongly linked to insulin resistance, obesity, gut microbiome dysbiosis, and genetic susceptibility factors. The escalating epidemics of obesity and type 2 diabetes have substantially contributed to the increasing disease burden of NAFLD. While considerable progress has been achieved in elucidating NAFLD pathogenesis, identifying potential therapeutic targets, and advancing pharmaceutical development, no pharmacologic agents have received regulatory approval for NAFLD treatment. Current management strategies emphasize lifestyle modifications, including weight reduction and dietary interventions, along with treatment of associated metabolic comorbidities. Guideline-based recommendations support the judicious use of pioglitazone and vitamin E in selected patient populations. This review comprehensively examines the pathogenic mechanisms and risk factors underlying NAFLD and NASH, providing insights to inform the development of targeted therapeutic strategies and improved diagnostic modalities.

Keywords

Non-Alcoholic Fatty Liver Disease, Risk Factors, Pathogenesis, Weight Management, Pharmacotherapy

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1. 引言

非酒精性脂肪性肝病是遗传易感个体由于营养过剩和胰岛素抵抗(Insulin Resistance, IR)引起的慢性进展性肝病, 疾病谱包括非酒精性脂肪肝(Non-Alcoholic Fatty Liver, NAFL)、非酒精性脂肪性肝炎(Non-Alcoholic Steatohepatitis, NASH)及其相关纤维化和肝硬化[1][2]。NAFLD 在各大洲都非常普遍, 据报道, 南美洲(31%)和中东(32%)的发病率最高, 其次是亚洲(27%)、美国(24%)和欧洲(23%), 而 NAFLD 在非洲不太常见(14%) [3]。此外, 预计到 2030 年, 亚太地区的 NAFLD 患者死亡率将增加 65%至 100% [4]。NAFLD 与能量密集型饮食、不良生活习惯、遗传变异、代谢综合征(MetS)、肥胖(尤其是腹型肥胖)、2 型糖尿病、高血压、高脂血症等相关。NAFLD 和 NASH 的发病机制目前尚不明确, 传统的“二次打击学说(即在单一脂肪变性基础上, 遭遇氧化应激等因素的二次打击)”已经过时。因为致病因素不可能在所有患者中都相同, 所以疾病的发病机制和临床表现都是高度异质性的[5]。近年来, 随着对疾病本质认识的深化, 国际肝病学术界推动术语从“非酒精性脂肪性肝病(NAFLD)”更新为“代谢相关脂肪性肝病(Metabolic-Associated Fatty Liver Disease, MASLD)”。这一变更强调疾病与代谢紊乱的核心关联, 摒弃“非酒精”这一排除性定义, 更贴合疾病的多重代谢病理生理机制。新定义要求患者至少具备一项心血管代谢危险因素(如肥胖、2 型糖尿病、高血压等), 从而更有利于早期识别、风险分层与个体化管理。MASLD 的提出不仅统一了临床诊断标准, 也为未来临床试验入组、药物研发及公共卫生策略制定提供了更科学的框架 [6] [7]。

2. 危险因素

2.1. 人口学特征和生活方式

NAFLD 或 NASH 在患病率和严重程度方面呈现出随年龄变化的性别差异[8]。在育龄期, 男性 NAFLD 患病率通常高于女性[9]-[12], 且病情容易进展到更严重的阶段, 如 NASH、肝硬化和 HCC [13]。然而, 在 50 岁以后, 女性的 MASLD 患病率与男性相似[14]。一些食物成分, 如饱和脂肪和果糖, 已被报道与 NAFLD 的发展密切相关[15]。果糖促进脂肪生成, 阻碍线粒体脂肪氧化, 导致线粒体尿酸生成增加和三磷酸腺苷耗竭, 从而引发氧化应激等一系列反应[16][17]。一项纵向研究结果表明, 对于非饮酒人群, 吸烟是与脂肪肝发病相关的一个重要风险因素, 在调整了潜在的混杂因素后, 这种显著的关联仍然存在。不饮酒者的脂肪肝发病率随着吸烟次数的增加而显著增加[18]。此外, 有研究提示口腔卫生习惯[19]、碳酸饮料摄入量[20]也与 NAFLD 相关。

2.2. 遗传多态性

一些研究已经证实了 NASLD 和纤维化的遗传性[21]。同时, 针对双胞胎和一级家庭成员的前瞻性研究已经确定了肝脏脂肪变性和纤维化的家族聚集性[22]。NAFLD 最常见的相关遗传变异是 *paatin* 样磷脂酶结构域蛋白 3 基因(PNPLA3)和跨膜 6 超家族成员 2 (TM6SF2)的基因变异。许多研究强调了 PNPLA3 的单核苷酸多态性(SNP), 其中 c.444C>G SNP 编码了与进行性肝纤维化和肝细胞癌相关的 I148M 变异[23]-[25]。TM6SF2 相关变异基因参与了谷丙转氨酶(ALT)的升高和肝脂肪变性程度的加重[26]。此外, 其他几个基因位点也与 NASLD 有关。MBOAT7 基因催化磷脂酰肌醇的酰基链重构, 其变异基因 MBOAT7 rs641738 与游离多不饱和脂肪酸增加有关[27]。相反, HSD17B13 中的一个变异基因(rs72613567)能够延缓 NASH 与晚期纤维化的进展[28]。此外, 一项大型基因组研究发现了 17 个位点, 包括涉及脂肪合成、线粒体功能和胆固醇代谢的新变异位点(例如 TOR1B、COBL 或者 GRB14、INSR、SREBF1 和 PNPLA2) [29]。

2.3. 临床疾病

肥胖(尤其是内脏肥胖)和 2 型糖尿病(T2DM)是 NASLD 的重要危险因素, 并有助于其进展为晚期纤维化、肝硬化和 HCC [30]。肥胖或高体重指数(BMI)与 NAFLD 以剂量依赖的方式密切相关, 体重指数每增加一个单位, 发生 NAFLD 的风险增加约 20% [31]。重要的是, 在肥胖和瘦型 NAFLD 患者中, 肝脏病变的组织学严重程度被证明是显著的[32]。一项回顾性队列研究证实了瘦型 NAFLD 患者的内脏型肥胖与 NASH 和晚期纤维化有关[33]。T2DM 患者中 NAFLD、NASH 和晚期肝纤维化的全球患病率估计分别为 55.48%、37.33%和 17.02% [34]。NAFLD 患者的糖尿病前期/糖尿病状态与严重肝脂肪变性(OR 2.00, $P < 0.005$)、严重小叶炎症(OR 2.25, $P < 0.005$)、严重肝脂肪变性(OR 2.00, $P < 0.005$)、肝球囊化(OR 1.54, $P = 0.069$)和显著纤维化(OR 1.30, $P = 0.45$)有关[35]。有研究表明 T2DM 是肝纤维化的独立危险因素[33], 即使在瘦型 NAFLD 患者中, T2DM 也能有效预测肝纤维化[36]。肠道微生物组及其组成部分在人类健康中发挥着重要作用, 肠道微生物失调与 NASLD 和肝纤维化的发展和严重程度之间存在关联[37]。肥胖可导致阻塞性睡眠呼吸暂停(OSA)和 NAFLD, OSA 也可独立影响 NAFLD 的发生和进展[38]。肌肉减少症被定义为肌肉质量及其力量的进行性损失, 其与 NAFLD 以双向方式相关[39], 独立于胰岛素抵抗(IR)或肥胖[40]。此外, 多囊卵巢综合征(PCOS)、高尿酸血症、甲状腺功能减退和自身免疫性甲状腺炎、银屑病和银屑病关节炎及牛皮癣也是 NAFLD 的危险因素[41]。

3. 发病机制

目前 NAFLD 的发病机制尚不明确, 多数学者比较认可的是“多重打击”学说, 认为是在肥胖、高脂

饮食、胰岛素抵抗(IR)的第一重打击下,慢性炎症、氧化应激反应、肠道菌群改变等共同作用下,导致了NAFLD的发生发展。

3.1. 过量的能量传递和新生脂肪生成

肝脏脂肪聚积主要与白色脂肪组织(WAT)分解导致游离脂肪酸外排增加和新生脂肪生成有关,同时过量的脂肪累积超过了肝脏的氧化和输出能力,导致脂毒性物质的产生,从而诱导内质网(ER)应激和线粒体功能障碍[42]。而脂肪组织中的胰岛素抵抗会导致脂肪分解失调和向肝脏输送的脂肪酸增加[43]。有研究表明,NAFLD患者肝脏脂质含量的增加主要归因于葡萄糖和果糖参与的脂肪从头生成途径(DNL)[44]。过量的果糖传递导致肝脏细胞内ATP的消耗,阻断蛋白质合成,诱导氧化应激和线粒体功能障碍,同时果糖磷酸化这一过程并不受负反馈机制调节[45]。几乎门静脉血液中的所有果糖都经历磷酸化和随后的从头脂肪生成。

3.2. 胰岛素抵抗

胰岛素抵抗削弱了对肝脏糖异生的抑制,导致高血糖和高胰岛素血症,并促进游离脂肪酸向肝脏持续慢性过量输送[46]。即使在正常体重且无T2DM的NAFLD患者中,骨骼肌和肝脏也存在着胰岛素抵抗,胰腺胰岛素分泌的增加、肝脏胰岛素清除率的降低及代偿性的门静脉高胰岛素血症也只能部分抑制肝脏糖异生和脂肪组织脂解[47]。SREBP-1和ChREBP是由胰岛素和碳水化合物激活的转录因子,并调节促进新生脂肪生成的酶[48]。胰岛素对极低密度脂蛋白(VLDL)产生的抑制作用减弱,导致甘油三酯和低密度脂蛋白的过量产生[49]。胰岛素抵抗与肝内脂质累积密切相关,目前的研究强调了脂质中间体(如神经酰胺)的作用,它们可诱导内质网应激和线粒体功能障碍,并可能介导胰岛素抵抗[50]。

3.3. 肠道微生物生态失调

多项研究表明,肠道微生物失调与NAFLD的发展和严重程度以及肝纤维化之间存在关联[37]。肠道微生物群可能通过几种潜在机制促进NAFLD,包括肠道通透性增加(引发脂多糖易位及全身性炎症)、肠道微生物多样性减少、能量调节中断、以及微生物代谢物(如乙醇、乳酸)和内毒素的产生[51]。细菌门之间的不平衡,导致脂多糖(LPS)和促炎细胞因子(如TNF- α 、IL-6)水平升高。这些炎症介质激活了TLR4/NF- κ B、AMPK信号通路,从而促进肝脏脂肪变性和炎症[52]。Kupffer细胞是肝脏的常驻巨噬细胞,对肠道微生物群的变化特别敏感,当LPS水平增加时,它们向M1促炎表型极化,这种极化会显著放大肝脏炎症和氧化应激[53]。

4. 治疗

目前没有药物治疗被批准专门治疗NAFLD。药物降糖、降脂和天然胆汁酸治疗已被用于治疗NAFLD,但存在缺陷[54]。生活方式干预、饮食和运动是目前治疗NAFLD的推荐干预措施。

4.1. 保守治疗——改变生活方式和减轻体重

减肥仍然是MASLD患者管理的基石。根据组织学,体重减轻5%与肝脏脂肪减少和肝损伤改善有关;而体重减轻超过7%可改善NASH活动度;减重超过10%,可逆转肝纤维化[55]。在饮食方面,为了达到减肥效果,建议女性每天1200千卡的热量摄入,男性则建议每天摄入1400~1500千卡食物[56]。在众多饮食方案中,美国、欧洲和亚洲的主流协会推荐NAFLD患者选用地中海饮食(富含水果、蔬菜、全谷物和不饱和脂肪),其对心血管有益,并促进肝脏、心脏和胰腺的脂肪动员[57]。同时,摄入适量的维生素E、咖啡因和多酚可能也对治疗NAFLD有益[58]。无论是否进行饮食干预,所有的运动方式和运动

强度都对 NAFLD 有益, 运动已被证明可以减少肝脂肪变性, 降低肝酶、血糖, 并改善血脂[59]。推荐最少每周 150 分钟的中等强度体力活动或每周 75 分钟的高强度体力活动[1]。有氧与抗阻训练结合效果最佳; 高强度间歇训练(HIIT)在肝脂肪减少方面优于中等强度持续训练[59]。对于因关节和心肺合并症而难以进行有氧运动的患者, 阻力训练是一种可接受的替代方案, 而对于身体健康的个体, 建议将有氧和阻力训练相结合[60]。

减肥手术现在被推荐为治疗临床重度肥胖及其并发症的有效方法[61], 主要包括 Roux-en-Y 胃旁路术或袖式胃切除术。多项荟萃分析显示, 减肥手术后 NASH 缓解率可达 70%~85%, 纤维化逆转率约 30%~40% [61] [62]。手术适应症因国家或地区而异, 美国协会建议 BMI ≥ 35 kg/m² 或 BMI ≥ 30 kg/m² 伴 T2DM, 欧洲协会建议 BMI ≥ 40 ~50 kg/m² 或 BMI ≥ 35 kg/m² 伴合并症, 而韩国肥胖管理学会和中国糖尿病学会, 则建议在合并症存在的情况下降低 BMI 阈值(≥ 27.5 kg/m²) [63]-[66]。根据肝活检, 减肥手术改善了 30%病态肥胖患者的脂肪变性、NASH 和肝纤维化[62]。然而, 约 5%~10%的患者术后出现 NAFLD/NASH 复发或加重, 尤其是在体重反弹、持续高胰岛素血症或遗传易感(如 PNPLA3 变异)人群中[67][68]。因此, 术前应综合评估 BMI、合并症、肝纤维化程度、遗传背景及患者意愿, 制定个体化手术方案[63]-[66]。

4.2. 药物治疗

与 NASH 和 NAFLD 相关的多因素病理生理过程需要实施综合治疗策略以获得有效治疗。针对三个关键病理领域, 即脂质代谢和脂毒性、氧化应激和炎症、胰岛素敏感性和葡萄糖稳态, 为管理这些复杂疾病提供了一种战略方法[69]。

Resmetirom 是第一个, 也是目前唯一一个获 FDA 批准的用于治疗 NASH 的药物[70]。虽然甲状腺激素的肝外作用主要通过甲状腺激素受体 α (THR- α)介导, 但甲状腺激素受体 β (THR- β)是肝脏中甲状腺受体的主要形式[71]。在 NASH 中, THR- β 作用受损, 导致线粒体功能降低、脂肪酸 β -氧化减少和纤维化增加[70]。而 Resmetirom 作为(THR- β)的选择性激动剂, 靶向作用于肝脏, 通过降低脂肪毒性和改善肝细胞线粒体功能, 可能达到抗炎和抗纤维化的作用[70]。其关键 III 期临床试验(MAESTRO-NASH)结果显示, 在接受 Resmetirom 治疗 52 周后, NASH 缓解且纤维化无恶化的患者比例显著高于安慰剂组(25.9% vs. 9.7%, $P < 0.0001$); 同时, 纤维化改善 ≥ 1 级且 NASH 未恶化的患者比例也显著提高(24.2% vs. 14.2%, $P = 0.0002$)。此外, Resmetirom 还显著降低了患者的肝脏脂肪含量(通过 MRI-PDFF 评估)和肝脏硬度(通过 FibroScan 评估) [72]。该药物最常见的不良反应为轻度至中度的腹泻和恶心, 总体耐受性良好, 未出现明显的安全性信号[72]。然而, 其长期有效性与安全性仍需进一步观察[72]。此外, 其他治疗 NAFLD/NASH 的药物也在研究中, 主要包括 PPAR 激动剂、FXR 激动剂、胰高血糖素样肽-1 (GLP-1)受体激动剂、成纤维细胞生长因子(FGF)类似物等。奥贝胆酸(OCA)作为 FXR 激动剂, 其在 III 期 REGENERATE 研究中显示出显著的抗纤维化效果, 但因瘙痒副作用和高 LDL-C 升高风险, 未能获得 FDA 全面批准, 仅限用于部分特定患者[73]。司美格鲁肽(Semaglutide)属于 GLP-1 受体激动剂, 在 II 期研究中显示出良好的 NASH 组织学改善效果, 但在 III 期研究中未能达到主要终点, 提示单纯降糖减重可能不足以逆转所有 NASH 患者的纤维化进程[74]。Lanifibranor (PPAR α/δ 激动剂)和 FGF21 类似物在 II 期研究中表现出改善 NASH 组织学的潜力, 目前正推进至 III 期临床, 其多重机制(抗炎、改善胰岛素敏感性、促进脂肪酸氧化)被认为是其优势所在[75]。

一些针对肠道微生物组的治疗策略正在被探索用于治疗 MASLD, 有可能延缓 NAFLD 病情的进展[76]。临床研究显示益生菌(如乳酸菌、双歧杆菌)能降低肝脏脂肪含量及改善肝酶水平[77]。合成益生菌将益生菌与菊粉、低聚果糖(FOS)等益生元结合在一起, 通过为有益菌提供支持性环境, 从而改善肠道菌

群组成和减少肝脏脂肪堆积[78]。粪便微生物群移植(Fecal Microbiota Transplantation, FMT)是另一种创新方法, 通过转移健康供体的粪便物质来恢复患者肠道微生物的菌群平衡, 已被证明能改善胰岛素敏感性和减少肝脏脂肪累积[79]。

5. 总结与展望

NAFLD 是世界范围内的公共卫生问题。由于 NAFLD 的发病机制是多因素的, 因此应该根据患者的遗传背景、年龄、性别、BMI 等因素, 以及是否存在其他临床合并症, 制定个性化的疾病监测和疾病治疗方案。在治疗方面, 改变饮食习惯和获得足够强度的运动仍是目前临床上治疗 NAFLD 的主要方式。同时, resmetiron 似乎是有前景的治疗药物, 然而其他药物及多种药物联合治疗的疗效如何, 还需要更多研究来进一步阐明。

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