

2型糖尿病与非酒精性脂肪性肝病：关联与管理

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摘要

非酒精性脂肪性肝病(NAFLD)已成为全球范围内一个主要的公共卫生问题,同时也是最常见的慢性肝病,其患病率和发病率正迅速增加。尽管NAFLD在普通人群中相当普遍,但仅有少数NAFLD患者会进一步发展为非酒精性脂肪性肝炎(NASH),并可能伴随晚期肝纤维化(即3~4期纤维化)和肝脏相关的并发症。值得注意的是,2型糖尿病患者被认为是罹患NASH和晚期纤维化的高风险人群。当前,医学指南建议对2型糖尿病患者进行NAFLD筛查,并评估其纤维化的风险。本文旨在阐述2型糖尿病与NAFLD之间的紧密联系,并探讨相关的管理方法。

关键词

非酒精性脂肪性肝病, 2型糖尿病, 关联, 管理

Type 2 Diabetes Mellitus and Nonalcoholic Fatty Liver Disease: Correlation and Management

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Abstract

Nonalcoholic Fatty Liver Disease (NAFLD) has emerged as a major global public health issue and the most common chronic liver disease, with rapidly increasing prevalence and incidence. While

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NAFLD is prevalent in the general population, only a fraction of patients with NAFLD progress to nonalcoholic steatohepatitis (NASH), potentially accompanied by advanced liver fibrosis (stages 3~4 fibrosis) and liver-related complications. Notably, individuals with type 2 diabetes mellitus (T2DM) are considered to be at a high risk of developing NASH and advanced fibrosis. Current medical guidelines recommend screening for NAFLD in individuals with T2DM and assessing their risk of fibrosis. This article aims to elaborate on the close association between T2DM and NAFLD and explore relevant management approaches.

Keywords

NAFLD, T2DM, Correlation, Management

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1. 引言

目前, 非酒精性脂肪性肝病(NAFLD)已成为慢性肝病的主要原因, 影响全球四分之一的成年人[1], 在世界范围内造成了沉重负担。NAFLD 更严重的形式为非酒精性脂肪性肝炎(NASH), 其特征主要为小叶坏死性炎症, 伴或不伴小叶中心纤维化, 可进展为肝硬化甚至肝细胞癌。NAFLD 的死亡率或肝脏相关临床结果的最重要预测因素是晚期纤维化的存在, 包括桥接纤维化(3期)和肝硬化(4期) [2]。值得注意的是, 在 2 型糖尿病群体中, 超过 1/3 的患者同时患有 NASH, 而约 1/6 的患者已出现进展期纤维化[3]。2 型糖尿病通过多种机制促进了 NASH 和晚期纤维化的发展[4]。虽然肝活检目前仍是 NAFLD 诊断和分级的金标准, 但其侵入性的操作方式限制了广泛应用。因此, 临床实践中更倾向于使用血清生物标志物或肝脏成像来筛查显著纤维化。经验证的无创性肝纤维化检测方法已在普通人群中成功识别出其他难以发现的肝脏疾病。在 2 型糖尿病合并 NAFLD 患者中, 采用无创性肝纤维化标志物进行慢性肝病的分层和晚期纤维化的识别尤为重要, 以确保将医疗资源集中于需求最迫切的患者。因此, NAFLD 的及时诊断、有效评估和管理对于防止疾病进展为晚期纤维化及其相关并发症具有至关重要的意义。本文的主要目的是探讨 2 型糖尿病与 NAFLD 之间的联系及相应的管理策略。

2. 2 型糖尿病患者的 NAFLD

目前的数据揭示, 2 型糖尿病与 NAFLD 之间的关系远比之前认为得要复杂。2 型糖尿病不仅是 NAFLD 的常见合并症, 更是推动 NAFLD 向 NASH 发展的决定因素之一[5]。根据多项队列研究的证据表明, 被诊断为 2 型糖尿病的患者中, NAFLD 的发病率显著上升, 患病率估计在 42.6%至 72.1%之间 [6]-[10]。普通的 NAFLD 患者中约 10%~20%可进展为 NASH, 但在同时患有 2 型糖尿病的情况下, NAFLD 进展为 NASH 的风险增加 2~3 倍[11] [12]。一项基于病理学结果的研究结果指出, 在 NAFLD 合并 2 型糖尿病的患者群体中, 高达 80%的病例在病理学上被诊断为 NASH, 而 30%~40%的病例已出现肝纤维化 [13]。这些数据进一步凸显了 2 型糖尿病在 NAFLD 进展中的重要作用, 以及合并 2 型糖尿病的 NAFLD 患者面临更高风险。

3. 病理生理机制

2 型糖尿病患者的特征主要表现为低度炎症和脂肪组织胰岛素抵抗。胰岛素在脂肪代谢中起着关键

作用, 通过促进脂肪的合成和贮存、抑制脂肪的分解来介导脂肪代谢[14]。在胰岛素抵抗(IR)的状态下, 胰岛素对脂肪动员的关键酶——激素敏感性甘油三酯脂肪酶(HSL)的抑制作用减弱, 促进脂肪水解, 游离脂肪酸(FFA)增多。一旦 FFA 超过肝脏代偿能力, 就会引发肝内脂肪变性[15]。为了代偿胰岛素抵抗, IR 患者体内胰岛素含量会上升, 形成高血糖和高胰岛素血症。这两种状况分别通过肝脏脂质代谢的调控基因——固醇调节元件结合蛋白-1c (SREBP-1c)与碳水化合物反应元件结合蛋白(ChREBP)诱导肝脏从头脂肪生成促进肝脏合成甘油三酯[16]。在正常情况下, 肝脏线粒体在脂肪酸 β 氧化下产生活性氧, 在多种抗氧化因子参与下, 氧化与抗氧化处于平衡状态。过量的 FFA 会导致线粒体功能性应激, 刺激 Kupffer 细胞, 并激活诸如 JUK 等炎症通路, 这些通路能够直接抑制胰岛素受体底物磷酸化而影响胰岛素作用, 进而加重肝脏 IR、损害肝脏脂质氧化, 并推动 NASH 和纤维化的发展[17] [18]。脂肪组织是一种良好的内分泌器官, 分泌成为脂肪因子的激素和细胞因子。脂肪组织功能障碍与胰岛素原(脂联素、瘦素)和抗胰岛素(即 TNF α)细胞因子之间的失衡密切相关[19]。促炎脂肪因子能激活 JNK 和 NF- κ B 通路, 激活炎症通道后会进一步加重肝脏 IR, 使得肝细胞受损更为严重。脂联素在调节脂肪酸氧化、抑制 FFA 的积累、维持全身的葡萄糖稳态和肝脏胰岛素敏感性方面发挥着重要作用。其循环水平与纤维化进程呈负相关, 而低循环水平的脂联素与 2 型糖尿病有关[20]。另一方面, 瘦素在促进肝星状细胞活化、肝纤维化以及控制能量平衡和抑制食欲方面起作用[21]。2 型糖尿病患者肠道菌群会发生显著改变, 这可能导致肠道屏障功能受损和内毒素的释放。这些肠道源性内毒素经模式受体识别对 LPS-CD14-TLR4 信号通路产生介导, 将肝 Kupffer 细胞激活, 引起炎症反应和肝脏损伤, 进而促进 NAFLD 向 NASH 及晚期纤维化的进展[22]。

4. T2DM 合并 NAFLD 的筛查与肝纤维化无创评估

晚期纤维化是 NAFLD 长期预后的关键决定因素, 并且与较高的总死亡率有关, 因此在病程早期识别高危患者对于预防及检测肝脏相关并发症的风险至关重要[23]。美国、亚太地区及我国最新的相关指南均建议对 2 型糖尿病患者进行 NAFLD 常规筛查及晚期纤维化评估[24]-[26]。

4.1. 筛查

肝酶的变化与肝脏脂肪病变程度并不总是相符的, 不推荐使用肝酶筛查 2 型糖尿病中 NAFLD 的患病情况[27]。肝活检仍然是评估疾病活动严重程度和肝纤维分期的金标准。然而肝活检属于侵入性操作, 并且成本较高, 不是常规筛查的实用一线方法。临床上最常使用普通超声对 2 型糖尿病患者筛查 NAFLD, 但其对轻度脂肪变性敏感性较低, 晚期纤维化也会影响观察所见[28]。通过振动控制瞬态弹性成像(TE)进行受控衰减参数(CAP)测量是比超声检查更灵敏的工具, 能快速检出、区分轻度和中-重度肝脂肪变性。TE 的准确性随着体重指数(BMI) > 30 而降低, 肥胖患者需慎重解释受控衰减参数(CAP)值[29]。氢质子磁共振波谱分析(^1H -MRS)能够准确检测 $\geq 5\%$ 肝脂肪变性, 但受成本限制, 目前主要应用于临床研究领域[28]。

4.2. 无创评估

血清转氨酶在不同的情况下通常升高, 但在 NAFLD 的严重阶段也可能在正常范围内。在 2 型糖尿病合并 NAFLD 患者中, 需要使用非侵入性检测的方法来对慢性肝病进行晚期纤维化风险分层。现有非侵入性检测包括: 纤维化评分模型、血液生物标志物、瞬时弹性成像。尽管这些非侵入性工具并不能完全消除肝活检的需要, 但它们大大减少了需要肝活检的患者数量。

4.2.1. 无创纤维化评分

NAFLD 纤维化评分(NFS)可通过年龄、BMI、丙氨酸氨基转移酶/天冬氨酸氨基转移酶比值、血小板计数、白蛋白、以及是否合并空腹血糖受损和糖尿病测值来评估 NAFLD 患者肝脏纤维化程度[30]。通过

计算两个诊断临界值(-1.455 用于排除进展性纤维化, 0.676 用于纳入进展性纤维化), 帮助确认肝纤维化的进展程度[31]。然而当使用 NFS 评估 2 型糖尿病人群中的进展性纤维化病例时, 排除率显著降低 3%~13% [32]。NFS 的效用还受到年龄、BMI 的限制, 导致不确定结果的高患病率。

FIB-4 评分基于常见临床参数, 包括年龄、天冬氨酸氨基转移酶、丙氨酸氨基转移酶和血小板计数[33], 这些参数易于获取并且可以在常规就诊期间进行计算。对于 NAFLD, FIB-4 < 1.3 提示晚期纤维化风险很小。FIB-4 在使用较低的临界值时对晚期纤维化的阴性预测值很高, 适合排除晚期纤维化, 可用于筛查糖尿病前期和 2 型糖尿病患者[34]。

4.2.2. 血清生物标志物

增强型肝纤维化(ELF)测试是一种结合血清中透明质酸、金属蛋白酶组织抑制因子 1 和 III 型前胶原肽三个指标进行计算的肝脏基质代谢直接标志物。ELF 测试在评估肝纤维化方面表现出良好的诊断准确性, 并且可以预测疾病进展和肝脏相关临床事件的发展, 如腹水、静脉曲张出血和肝细胞癌[35]。

4.2.3. 瞬时弹性成像

瞬时弹性成像(TE)探针将声波发送到肝脏组织, 声波通过同质组织的传播速度与其弹性成正比, 弹性与肝纤维化的程度相关, 从而量化肝纤维化[36]。TE 测量获得肝纤维化程度(也称为弹性(E), 以 Kpa 表示)。根据 E 值的范围, 可以将肝纤维化分为不同的阶段。目前用于临床的 TE 设备以 FibroScan 及 FibroTouch 应用较多, 前者 LSM ≥ 15.0 kPa 考虑肝硬化, LSM ≥ 11.0 kPa 考虑进展期肝纤维化, LSM < 10.0 kPa 考虑排除肝硬化, LSM < 8.0 kPa 考虑排除进展期肝纤维化, LSM 处于 8.0~11.0 kPa 患者需接受肝活组织学检查明确肝纤维化状态; 而后者诊断肝纤维化建议界值可靠性仍待更多临床研究确认[37]。LSM < 8 kPa 对排除进展型纤维化($\geq$ F3-F4)具有很好的阴性预测价值[22]。TE 阈值还需要在糖尿病和多种族队列中进行临床试验得到验证。

在评估过程中, 可以先通过简单的无创纤维化评分来排除晚期纤维化。对于评分为中高危的患者, 还需进一步行血清生物标志物或瞬时弹性成像评估。若患者经 ELF 或 TE 评估为低风险, 则可在 2~3 年后进行重复评估。而对于高风险或不确定风险的患者, 应及时转诊至消化内科或肝病专科进一步评估, 包括进行肝活检[24] [25]。

5. 治疗

由于 NAFLD 复杂的机制, 目前尚无特定的治疗药物获得批准。当前的研究重点在于探究新的、有前景的治疗方案来应对 NAFLD。在现有的 NAFLD 相关指南中, 主要强调生活方式的调整。常用的治疗方式包括饮食控制、运动、减重手术以及药物治疗(降糖药物)等。饮食热量限制是关键。NAFLD 患者往往倾向于食用高热量、高糖、富含饱和脂肪酸及胆固醇的食物, 而新鲜果蔬、多不饱和脂肪酸及富含纤维的食物则摄入不足[38]。地中海饮食对肝转氨酶、体重指数及 IR 改善均有较好的作用, 被证实可防治肥胖、2 型糖尿病、NAFLD, 并降低全因死亡率[39]。通过生活方式干预或减肥手术减轻体重, 可以逆转脂肪性肝炎甚至纤维化。研究显示, 体重较基线下降 > 7% 时能够改善肝脏慢性炎症环境, 下降 > 10% 时能逆转肝纤维化[40]。目前的指南支持, 2 型糖尿病合并 NAFLD 的治疗, 应依据患者自身具体情况来选择合适的药物, 如吡格列酮、GLP-1 受体激动剂、SGLT-2 抑制剂、二甲双胍, 而目前不推荐使用 DPP-4 抑制剂治疗 2 型糖尿病合并 NAFLD [41]。

6. 结语

2 型糖尿病与 NAFLD 之间的关系错综复杂, 它们之间的相关影响不仅加剧了疾病的进程, 还给治疗带来了挑战。2 型糖尿病患者往往伴随着胰岛素抵抗和高血糖, 这些因素都可能促进脂肪在肝脏内的积

累,从而加速 NAFLD 的发展。在 2 型糖尿病合并 NAFLD 的患者中,晚期纤维化的风险显著增加,这一点尤为重要。纤维化是肝脏对慢性损伤的反应,它可能导致肝功能衰竭和门脉高压等严重后果。因此,对这类患者进行及时、准确的筛查和评估至关重要。已开发并被验证的几种无创生物标志物模型,可以识别或排除晚期纤维化。将这些模型评分与影像学检查结合使用更合适。通过这种综合评估,我们可以更准确地判断患者的病情,并制定个性化的治疗方案。

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