

非酒精性脂肪肝病和血管疾病：临床证据与机制回顾

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摘 要

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是全球肝病负担日益加重的重要原因。全世界约有25%的成年人可能受到NAFLD的影响。由于NAFLD通常与肥胖、2型糖尿病或高血压等代谢合并症(metabolic syndrome, MetS)相关, 因此通常被认为是MetS的肝脏表现。NAFLD和MetS之间的关联已经确定, 但仍需要证明NAFLD对血管风险和心血管疾病(cardiovascular disease, CVD)进展的独立影响。值得注意的是, 越来越多的证据表明, NAFLD患者患冠心病、心肌病和心律失常的风险很高, CVD是NAFLD患者死亡的主要原因。在本综述中, 我们讨论了NAFLD患者血管损伤的病理驱动因素。此外, 还将讨论NAFLD对亚临床和临床CVD的发生, 严重程度和进展的影响。最后, 描述了在该高危人群中筛查CVD的当前和潜在前景。

关键词

非酒精性脂肪肝, 心血管疾病, 代谢综合征

Nonalcoholic Fatty Liver Disease and Cardiovascular Disease: Clinical Evidence and a Mechanistic Review

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Abstract

Nonalcoholic fatty liver disease (NAFLD) is an important cause of the increasing burden of liver

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disease worldwide. About 25% of adults worldwide may be affected by NAFLD. Because NAFLD is often associated with metabolic comorbidities (MetS) such as obesity, type 2 diabetes, or hypertension, it is generally considered a hepatic manifestation of MetS. The association between NAFLD and MetS has been established, but there is still a need to demonstrate the independent effect of NAFLD on vascular risk and cardiovascular disease (CVD) progression. Notably, there is growing evidence that patients with NAFLD are at high risk of coronary heart disease, cardiomyopathy, and arrhythmias, and that CVD is the leading cause of death in patients with NAFLD. In this review, we discuss the role of NAFLD as an emerging risk factor for CVD, outlining the pathological drivers of vascular injury in patients with NAFLD. In addition, the impact of NAFLD on the occurrence, severity, and progression of subclinical and clinical CVD will be discussed. Finally, the current and potential prospects for screening for CVD in this high-risk population are described.

Keywords

Non-Alcoholic Fatty Liver, Cardiovascular Diseases, Metabolic Syndrome

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1. 介绍

非酒精性脂肪肝病(nonalcoholic fatty liver disease, NAFLD)是全球慢性肝病的最常见原因,在成年人中的患病率已高达 30%,这造成巨大的临床和经济负担[1]。NAFLD 与动脉粥样硬化性血脂异常、腹部肥胖、高血压和糖耐量受损等多项代谢综合征(metabolic syndrome, MetS)的特征密切相关,通常被认为是 MetS 的肝脏表现[2]。NAFLD 患者的死亡率远高于一般人群,心血管疾病(cardiovascular disease, CVD)是 NAFLD 患者最常见的并发症和死因[3] [4]。与未患有 NAFLD 的患者相比,被诊断为 NAFLD 的患者在 10 年内发生心血管事件的倾向显著升高。根据弗雷明汉评分,患有 NAFLD 的男性平均心血管风险为 16.0%,而没有患 NAFLD 的男性为 12.7%。同样,患有 NAFLD 的女性平均患心血管疾病的风险为 6.7%,而没有患 NAFLD 的女性为 4.6% [5]。NAFLD 本身是否代表心血管风险,是否是 MetS 的必然结果,还是两者的结合,目前仍存在争议。多项研究表明,NAFLD 是独立于传统心血管风险因素的心血管风险因素。特别是,最近的一项为期 14 年的队列研究表明,NAFLD 患者的主要不良心血管事件发生率显著提高[6]。与对照组相比,脑卒中发生率增加 1.58、充血性心力衰竭发生率增加 1.75、以及心血管死亡率增加 1.37 [6]。在本综述中,我们讨论了 NAFLD 和 CVD 的潜在病理生理机制,NAFLD 作为代谢功能障碍相关心血管危险因素的作用。此外,还将讨论 NAFLD 对亚临床和临床 CVD 的发生,严重程度和进展的影响。

2. 病理生理机制

NAFLD 和 CVD 都是 MetS 终末器官损伤的表现,NAFLD 中 CVD 发生的潜在机制尚不完全清楚,同时涉及许多不同的途径。内脏脂肪组织功能失调引起的腹型肥胖,在不良心脏代谢结局中起着核心作用[7]。内脏肥胖与循环中游离脂肪酸(free fatty acid, FFA)的慢性溢出有关,会诱发肝脏胰岛素抵抗。甘油三酯、小密度低密度脂蛋白和低密度脂蛋白颗粒的过量产生,这些物质都很容易滞留在外周血管,进而导致动脉粥样硬化血脂异常的发生[8]。腹型肥胖已被发现是上肢和下肢动脉疾病的独立危险因素[9]。同时,FFA 水平的升高有可能直接或间接激活肝糖异生,降低肝脏胰岛素敏感性。胰岛素敏感性的下降

导致极低密度脂蛋白的增加和高密度脂蛋白的减少,从而加速了动脉粥样硬化性血脂异常的循环[10]。

人们还普遍认识到,造成这种改变的机制可能与超重和肥胖无关。异位脂肪的积累以及随后来自脂肪的代谢物的释放和炎症途径的激活,在局部和系统水平上均引发了级联的病理生理改变,最终导致 NAFLD 和 CVD 的发生[11]。内脏脂肪组织作为一个自主的内分泌器官,释放脂肪因子(如肿瘤坏死因子- α 、白细胞介素-6 和白细胞介素-10),这些因子不仅会引起慢性炎症反应,而且可能影响肝细胞内的胰岛素信号通路并破坏胰岛素敏感性,促进了动脉粥样硬化性血脂异常的发展和肝细胞中 FFA 的积累[12] [13]。值得注意的是,性别差异带来的脂肪沉积可能部分解释了 CVD 风险的差异。在持续的体能训练测试中发现,女性优先动员脂肪储存,脂肪氧化供能更强,因此男性会比女性更容易出现内脏肥胖[14]。NAFLD 的流行病学特征也证实了这一性别差异,男性 NAFLD 患病率显著高于女性[15]。

大量的脂质在外周和肝脏内堆积,进而发生线粒体和内质网产生脂毒性应激,导致线粒体功能的改变和活性氧产生的增加[16]。一方面,内质网稳态的扰动和氧化应激已被证明通过诱导内皮功能障碍影响代谢性炎症,使 NAFLD 患者易发生心血管事件[17];另一方面,由此产生的氧化应激也通过脂质过氧化,促进多不饱和脂肪酸的脂质过氧化,并产生有毒的醛产物,引起脂质损伤,这些经过氧化修饰的脂质具有更强的致动脉粥样硬化作用[18]。一项针对 NAFLD 进展和消退的前瞻性队列研究进一步证实了脂肪堆积、氧化应激、胰岛素抵抗所营造的低度系统性炎症在 NAFLD 晚期病程中会产生血管结构和功能的不可逆性损伤[19]。内皮功能障碍是动脉粥样硬化发展的初始阶段,已被观察到富含甘油三酯的脂蛋白含有载脂蛋白 C3 能够通过半胱天冬酶-3 诱导替代 NLRP3 炎症小体和 Toll 样受体 8 和 2 的二聚化来激活人单核细胞中的 NLRP4 炎症小体[20]。NAFLD 还被发现与高凝状态有关。NAFLD 患者不仅对血栓栓塞事件的易感性增加,而且纤溶酶原激活剂抑制剂 1、纤维蛋白原和血管性血肿因子的血液浓度水平也有所升高[21] [22]。

随着近年来的研究发现,肠肝轴这一原本源于解剖学的概念,开始同样适用于分析 NAFLD 和 CVD 在发病机制上的功能学问题[23]。在 NAFLD 患者高果糖和高脂肪的饮食习惯导致的病理条件下,破坏了肠上皮屏障和肠道血管屏障的原有的功能和通透性,通过门静脉系统连接的肠肝轴,导致小肠细菌过度生长及细菌代谢物、内源性乙醇、胆汁酸-微生物串扰和脂多糖等内毒素进入肝脏及全身血液系统,最终发展为全身性低度炎症[24] [25] [26] [27] [28],参与了 AS 的发病[29]。一项荟萃分析强调,大肠杆菌、普氏菌、链球菌、粪球菌、粪杆菌和瘤胃球菌的丰度变化是 NAFLD 的普遍肠道细菌特征[30]。失衡的肠道细菌将左旋肉碱、胆碱和卵磷脂等含甲胺的营养素转化为三甲胺,肝脏中的黄素单加氧酶对其进一步加工成三甲胺 N-氧化物[31]。已有文章证实三甲胺 N-氧化物水平升高与发生动脉粥样硬化等重大不良心血管事件的风险增加有关[32] [33]。2019 年的一项在 34 名经活检证实为 NAFLD 患者中进行的临床队列研究发现三甲胺 N-氧化物还通过介导肝法尼样 X 受体信号传导来加重肝脂肪变性[34]。如此看来,循环中的三甲胺 N-氧化物水平与 NAFLD 的严重程度、动脉粥样硬化高度相关。

大规模的全基因组关联研究已经确定了与 NAFLD 易感性和其严重程度相关的特定基因,包括含有 patatin 样磷脂酶结构域 3 (PNPLA3)和跨膜 6 超家族成员 2 (TM6SF2)基因的多态性。TM6SF2 编码的蛋白质影响富含甘油三酯的脂蛋白的分泌和肝脂滴含量[35]。TM6SF2 野生型等位基因的携带促进甘油三酯和胆固醇分泌到循环中,总体上降低肝脏脂肪含量[36]。这些患者出现严重的血脂异常,这使他们患动脉粥样硬化的风险增加。有趣的是,PNPLA3 传变异的携带者往往具有明显的心脏保护表型。携带 PNPLA148 中的 I738409M 变体增加了肝脏脂肪含量,但可以预防 CVD [37]。然而,关于 NAFLD 患者心血管风险的遗传易感性的数据有限且尚无定论。最近一项双样本孟德尔随机化研究显示,遗传预测的 NAFLD 与冠状动脉疾病之间存在着强关联[38]。

本质上,NAFLD 中动脉粥样硬化的发病机制受到动脉粥样硬化性血脂异常、氧化应激、促炎环境、

高血糖、血栓前状态和遗传易感性的相互作用的复杂影响。

3. NAFLD 与亚临床血管疾病

亚临床血管疾病(subclinical vascular disease, SVD)能够帮助识别和预防过早死亡, 并且 SVD 的无创测量是老年人心血管事件的危险因素[39] [40]。SVD 的首发改变是内皮功能障碍, 之后出现动脉粥样硬化的形态学和功能学改变, 例如血管顺应性降低和颈动脉内中膜厚度(carotid intima-media thickness, CINT)增加。

在 NAFLD 中, 多种因素可能影响内皮功能, 例如致动脉粥样硬化性血脂异常、慢性低度炎症状态, 高血糖、氧化应激以及血栓前状态[41]。血管内皮功能障碍表现为内皮依赖性血管舒张受损、氧化应激升高、慢性炎症、白细胞粘附和通透性过高以及内皮细胞衰老。目前使用肱动脉的高频超声成像以评估内皮依赖性血流介导的血管舒张[42]。临床研究已经证实, 无论是否存在 MetS 的特征, NAFLD 患者的内皮依赖性血流介导的血管舒张均有所降低, 出现内皮功能受损[43]。此外, 在没有糖尿病, 病态肥胖和不受控制的高血压的情况下, 健康人群比经活检证实的 NAFLD 患者具有更好的内皮功能[44]。

动脉弹性特性是由血管壁中的胶原蛋白和弹性蛋白之间的比例决定, 并通过其生产和降解过程之间的动态平衡来保证血管最佳的弹性和顺应性。血管系统的老化与动脉壁结构属性的深层变化有关[45]。动脉硬度是动脉结构和功能的可靠特征, 大量的研究显示动脉硬度增加与许多心血管终点事件高度相关[46] [47] [48]。目前评估动脉僵硬度的方法很多, 研究中使用较多的有颈股搏波速度(cf-PWV)、臂踝脉搏波速度(ba-PWV)或颈动脉脉搏波速度(cPWV) [49]。与非 NAFLD 患者相比, NAFLD 患者的 ba-PWV 较高。即使在调整性别和年龄后, 同时患有 MetS 和 NAFLD 的患者的 ba-PWV 显著高于分别患有这两种疾病或均不患有这两种疾病的患者[50]。另一项荟萃分析显示, 与非 NAFLD 患者相比, NAFLD 患者的 cf-PWV, 增强指数和 ba-PWV 均显著增加[51]。

CINT 是用于检测亚临床动脉粥样硬化性血管疾病的最常用方法, 可作为临床试验中 CVD 风险的替代标志物。通过 CINT 定义的颈动脉粥样硬化和 NAFLD 之间的关联已在多项横断面与前瞻性研究中得到广泛证明[52]。NAFLD 脂肪变性的逐步增加会显著增加 NAFLD 发生颈动脉粥样硬化的风险。数据显示超过三分之一的患者患有颈动脉粥样硬化, 颈动脉粥样硬化的常规评估对于 NAFLD 至关重要[53]。NAFLD 患者的 CINT 显著高于非 NAFLD 患者, Logistic 回归显示 NAFLD 使 CINT 的比值比增加 35%, 与传统危险因素和 MetS 的存在无关[50]。通过 NAFLD 纤维化评分和组织学评估, 晚期纤维化分期与较高的 CINT 与之之间的有较强相关性[54] [55]。有趣的是, NAFLD 的遗传倾向似乎也会导致 SVD, 特别是已得到广泛研究的 PNPLA3。PNPLA3 基因负责编码脂联蛋白, 在脂细胞的脂质代谢调控中起着至关重要的作用。与突变型 GG 携带者和对照组相比, 野生型 CC PNPLA3 表型的个体表现更高的 CINT [56]。

总而言之, 有多种证据表明 NAFLD 与亚临床血管损伤的存在和进展相关, 独立于其他代谢危险因素。纤维化阶段还与血管疾病的严重程度相关, 有效的纤维化筛查可以防止 NAFLD 患者 CVD 的进展。

4. NAFLD 中的临床血管疾病和急性心血管事件

NAFLD 与突发的临床 CVD 的风险增加有关[57]。根据最近在瑞典进行的一项纵向研究发现, 与一般人群相比, NAFLD 的 CVD 的风险提高了 54% [58]。在接受冠状动脉造影的患者中, 与无 NAFLD 人群相比, NAFLD 患者与更严重的血管疾病(一个或多个冠状动脉狭窄)相关[59]。此外, NAFLD 的存在还与高风险斑块的存在和更快的疾病进展有关。研究表明, NAFLD 是高危冠状动脉斑块的独立预测指标, 并可能部分阐明冠状动脉事件的高易感性[60]。在脆弱的动脉粥样硬化斑块恶化或破裂, 导致急性冠状动脉综合征的情况下, NAFLD 的存在与不利的临床后果有关。对 360 例诊断为 ST 段抬高型心肌梗死的患

者进行的综合检查显示,与对照组相比,NAFLD 患者的住院死亡率和 3 年死亡率均增加[61]。晚期纤维化与 NAFLD 患者的 CIMT、颈动脉斑块的存在和动脉僵硬度呈正相关,独立于传统的心脏代谢危险因素和胰岛素抵抗[62]。

此外,越来越多的证据表明,NAFLD 与心律失常之间存在相关性,包括房颤,室性心律失常和心脏传导阻滞[63] [64] [65]。这种关联可归因于 NAFLD 的炎症性质,它导致体循环或心包脂肪组织内局部产生促炎介质。这些介质可以通过影响特定的离子通道来影响心肌,从而延长动作电位的持续时间,进而延长 QT 间期[66]。最近的一项研究让人们关注到这样一个事实,即晚期肝病患者往往在房颤的防治不足,这可能是由于对出血风险增加的担忧[67]。

除了功能性心脏改变外,在 NAFLD 患者中也经常观察到心脏结构异常。一些研究结果表明,NAFLD 与主动脉瓣硬化和二尖瓣环钙化有关,这可能有利于该人群发生功能相关的瓣膜疾病[68] [69]。此外,相当比例的 NAFLD 患者经历心肌重构,特别是左心室,常伴有收缩和/或舒张功能受损[70] [71]。这些结构异常反过来又成为心律失常的另一个诱发因素。在超声心动图指标方面,心脏几何结构改变和舒张功能障碍(舒张期后壁厚度、左心室质量、相对壁厚和左心房容积以及射血分数、E/A 比值)与 NAFLD 患者纤维化严重程度有关且独立于心脏代谢因素[72]。患有严重脂肪变性的患者在再灌注后表现出更高的心肌功能受损率。这些改变是左心室功能下降、梗塞面积增大和死亡率增加的有力预测因素[73]。然而,一项包含 279,013 名患者数据的大型荟萃分析并未证实与肝脏脂肪含量相关的缺血性心脏病风险[74]。

多项研究显示 NAFLD 与脑血管疾病之间存在关联[57] [75]。42.5%的急性缺血性脑卒中患者发生 NAFLD [76]。NAFLD 可能与更严重的中风和更差的结果有关使用肝脏瞬时弹性成像评估的肝脏硬度结果显示,显着纤维化的存在,肝脏硬度测量值每增加一个单位,中风风险就会增加 1.26 倍[77]。但是,另一项孟德尔随机化研究显示,NAFLD 对缺血性脑卒中的潜在致病影响可能局限于大动脉粥样硬化和小血管闭塞这两个亚型[78]。此外,还发现超声诊断的 NAFLD 可以预测急性脑干梗塞的严重程度和进展,急性脑干梗塞是与高度残余残疾相关的特殊中风亚组[79]。总体而言,没有足够的证据表明 NAFLD 与所有形式的中风的发生和严重程度相关。

最后,人们对微血管疾病与 NAFLD 之间的关联也越来越感兴趣,特别是作为这些患者慢性肾衰竭的常见原因[80]。众所周知,糖尿病和/或高血压本身就on容易引发多种微血管疾病。一项随访 4.6 年的中国队列研究显示,代谢功能障碍合并 NAFLD 与慢性肾脏病的风险增高有关,而与单纯 NAFLD 的相关性不大[81]。然而,一些研究表明,NAFLD 与微血管病相关,独立于传统的心血管危险因素[82]。此外,肝脏硬度与 NAFLD 患者肾脏结局可能存在着联系。荟萃分析结果显示,肝纤维化与 NAFLD 患者慢性肾脏疾病和白蛋白尿风险增高有关。一致的是,在一个由 1763 名中国糖尿病患者组成的大型队列中,晚期纤维化的存在(使用瞬时弹性成像检测)与肾病相关[83]。在本研究中,微量白蛋白尿的几率随着肝脏硬度测量值的增加而增加。

总之,越来越多的证据表明,代谢失调作为一个共同的因素,可以解释观察到的 NAFLD 与冠状动脉疾病、心律失常和结构性心脏病之间的相关性。因此,一个专家小组最近提出采用术语“MAFLD”(代谢功能障碍相关的脂肪肝疾病)作为一个更合适和更全面的描述符,准确地代表 NAFLD 的潜在机制[84]。

5. NAFLD 患者的血管疾病筛查与干预

CVD 是 NAFLD 患者发病和死亡的主要原因。CVD 和 NAFLD 之间的强相关性强调了在该人群中早期发现和适当治疗心脏代谢危险因素的必要性[85]。因此,指南建议 NAFLD 患者进行 CVD 风险综合评估,并根据个体情况每一到两年进行一次重新评估[86]。然而,尽管被归类为高危患者,但目前缺乏证据,需要坚持对 NAFLD 患者心血管危险因素的传统管理方法[87]。NAFLD 的纤维化阶段已被确定为决定预

后的一个重要因素[88]。大量研究表明, 纤维化的进展也可以作为 CVD 发展的预测因子, 其风险随着纤维化的进展成比例地增加[89] [90] [91]。对于 $F \geq 2$ 纤维化阶段的患者, 可以考虑进行 CVD 筛查, 因为晚期纤维化(F3-F4)患者面临更高的心血管事件死亡风险[92]。有研究评估了联合血液检测在预测 CVD 相关预后中的重要性。然而, 目前的证据体系还不足以建立筛查方案。此外, 在这一特定人群中, 缺乏支持传统心血管评分。值得注意的是, 由于止血活性的提高, 平均血小板体积已证明其在预测心血管事件方面的效用[93]。弗雷明汉后代研究是第一项表明 γ -谷氨酰转移酶(γ -glutamyl transferase, GGT)与 CVD 相关的流行病学研究[94]。GGT 与动脉粥样硬化斑块之间的关联已在普通人群中得到充分证实。在这项研究中, GGT 与较高的体重指数、血压、低密度脂蛋白胆固醇、甘油三酯和葡萄糖相关。特别是, 在调整心血管风险因素后, GGT 每增加一个标准差, CVD 风险和死亡率就会增加 13%和 26%。

生活方式的改变, 包括饮食改变、身体活动和减肥干预是 NAFLD 的一线治疗。在这种情况下, 最好采用实用方法, 将饮食限制与逐渐增加有氧或阻力训练相结合, 并应根据具体情况进行调整[95]。体重减轻对超重或肥胖 NAFLD 患者非常重要, 可通过限制热量、减肥手术或剧烈运动来实现[96]。体重减轻约 5%的总体重与肝脏脂肪含量显著降低约 30%和代谢异常的改善有关。然而, 为了显著减少肝细胞炎症, 至少减轻至少 7%至 10%可能是必要的。此外, 至少减轻总体重的 10%就需要解决与预后相关的纤维化[97] [98]。与以往的身体活动水平相比, 从事任何形式的身体活动或增加活动水平都比久坐不动的生活方式更可取。在被诊断为 NAFLD 的个体中, 体育活动表现出剂量 - 反应相关性, 其中高强度运动如跑步产生更有利的结果, 包括改善非酒精性脂肪性肝炎和纤维化[99]。在改善整体心脏代谢健康方面, 特别是阻力训练继承了有益的效果, 因为它以促进整体抗炎和抗动脉粥样硬化状态的方式影响身体成分[100]。适度的身体活动, 特别是与饮食干预相结合, 对减少内脏脂肪组织也有很大的影响。具体来说, 除了减少肝内脂肪外, 地中海饮食结合低碳水化合物消耗还能够进一步调动致动脉粥样硬化和糖尿病异位脂肪库, 例如心包内脂肪, 胰腺脂肪或皮下脂肪[101]。

总之, 虽然 CVD 仍然是 NAFLD 患者死亡的主要原因, 但目前没有足够的证据支持对这些患者实施筛查方案。尽管如此, 还需要进一步的前瞻性研究来确定非侵入性纤维化标志物在预测这一特定人群的心血管预后方面的效用。此外, 加强对 NAFLD 患者代谢危险因素管理的优化也势在必行。除了基于个人的方法外, 还迫切需要旨在减少久坐不动的工作时间和环境压力因素的负担的公共卫生干预措施, 例如公共建筑中的烟草烟雾, 非生理性光暴露(即蓝光), 环境噪音和空气污染, 并且对于使预防心脏代谢疾病更加全面非常重要[102]。

6. 结论

CVD 是 NAFLD 患者死亡的主要原因。无论是否存在常规代谢因素, NAFLD 都是 CVD 发展、严重程度和进展的危险因素。随着时间的推移, NAFLD 可能将极大地造成与 CVD 相关的健康问题的全球负担。近期在理解 NAFLD 和心血管风险之间关联的机制基础方面取得的进展, 可能有助于在该人群中实施对心血管风险的系统评估和管理。

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