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代谢功能障碍相关脂肪性肝病与心血管疾病：病理生理学机制

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摘　要

代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)是最普遍的慢性肝病之一，但MAFLD患者死于心血管疾病(cardiovascular disease, CVD)的频率高于肝脏疾病本身。与MAFLD相关的病理生理研究表明存在与CVD相关的潜在机制，涉及全身炎症、氧化应激、胰岛素抵抗(insulin resistance, IR)、糖脂代谢、肾素－血管紧张素系统(rein-angiotensin system, RAAS)和交感神经系统(sympathetic nervous system, SNS)、肠道微生物群以及遗传，促进CVD事件的发生。这篇综述分析了MAFLD和CVD之间的关系，概述了可能将MAFLD与CVD联系起来的潜在病理生理机制。

关键词

代谢功能障碍相关脂肪性肝病，心血管疾病，病理生理学

Metabolic Dysfunction-Associated Fatty Liver Disease and Cardiovascular Disease: Pathophysiological Mechanisms

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) is a common chronic liver disease, but patients with MAFLD are more likely to die from cardiovascular disease (CVD) rather than liver disease itself. Pathophysiological studies have shown that there are potential mechanisms associated with CVD in MAFLD, including systemic inflammation, oxidative stress, insulin resistance, glucose and lipid metabolism, the Renin-angiotensin system(RAAS) and sympathetic nervous system(SNS), the gut microbiota, and genetics. These factors contribute to the development of CVD events. This review aims to analyze the relationship between MAFLD and CVD and discuss the potential pathophysiological mechanisms that connect the two conditions.

Keywords

Metabolic Dysfunction-Associated Fatty Liver Disease, Cardiovascular Disease, Pathophysiology

1. 引言

非酒精性脂肪肝病(non-alcoholic fatty liver disease, NAFLD)被重新命名为 MAFLD，大约 99%的 NAFLD 患者也符合 NAFLD 诊断标准，所以现有 NAFLD 的文献同样适用于 MAFLD，新的定义强调了应伴有血糖调节受损、超重、高血压、高甘油三酯血症或血脂异常其中至少一种心脏代谢危险因素[1] [2]。研究表明，MAFLD 比 NFALD 更能识别 CVD [3] [4]。为避免混乱，本文均采用 MAFLD 进行阐述。

MAFLD 是一系列的肝脏疾病，其病程可变，从单纯性脂肪肝、代谢功能障碍性脂性肝炎(metabolic dysfunction-associated steatohepatitis, MASH)，最终导致肝硬化、肝细胞癌[5]；它是世界范围内最常见的肝脏疾病，最近的荟萃分析表明，在 2005 年或更早发表的研究中，MAFLD 的患病率为 26%，而 2016 年或更晚发表的研究中，MAFLD 的患病率为 38%，影响着世界上约三分之一的人口[6]；MASH 的经济负担很高，尤其是晚期疾病患者要承担累积的医疗费用，给社会带来巨大的健康和经济负担[7]。与 MAFLD 相关的多种共同的心脏代谢危险因素和 MAFLD 晚期纤维化的存在增加了 CVD 的风险[8] [9]。而且 CVD 是 MAFLD 患者的主要死亡原因[10] [11]，越来越多的证据表明，MAFLD 是导致 CVD 发生和/或进展的一个因素，包括心力衰竭(heart failure, HF)、冠状动脉粥样硬化性心脏病(coronary heart disease, CHD)和心律失常等[12] [13] [14] [15]。现有证据表明，25%至 40%的 MAFLD 患者患有 CVD，并且在 MAFLD 病人中，CVD 相关死亡所占比例高于肝脏相关死亡；这些发现强调了关注 CVD 在 MAFLD 患者中的重要性[16]。最近研究表明，尤其是 MAFLD 相关的肝脏炎症和纤维化以及由此导致的肝硬化是 CVD 发病和进展的最重要因素，成功地治疗该病可能有效地预防这些心脏代谢疾病的发生[17]。尽管在肝脏研究领域的学术研究者中，MAFLD 越来越被认为是 CVD 和许多其他代谢紊乱的重要危险因素，但 MAFLD 尚未被列为 CVD、糖尿病和血脂异常干预的主要目标。

2. 病理生理学

MAFLD 和 CVD 都是代谢综合征后期器官损伤的表现，CVD 和 MAFLD 通过多种病理生理机制相

关联[18]。潜在机制涉及与全身炎症、氧化应激、IR、糖脂代谢、RAAS 和 SNS、遗传以及肠道微生物群相关。

2.1. 炎症

代谢性炎症可被视为一种无菌状态，是肥胖、2 型糖尿病(T2DM)、CVD 和 MAFLD 发病机制的关键组成部分。肝脏、胃肠道和脂肪组织等不同区域是促炎驱动因素的重要来源，比如肿瘤坏死因子(TNF-a)、白细胞介素-6 (IL-6)、C 反应蛋白等[19] [20]；MAFLD 患者的循环炎症介质经常增加[18] [21]，影响心肌能量代谢、胎儿基因再表达、成纤维细胞增殖和金属蛋白酶激活，导致心脏功能障碍和左心室肥大[22]。比如，升高的 TNF-a 可以诱导活性氧物质(ROS)过量产生，ROS 的增加降低了心肌细胞中一氧化氮的生物利用度，然后抑制蛋白激酶 G 信号传导，导致心肌炎症反应[23] [24]。此外，ROS 可通过相关通路从而激活心脏重塑相关基因[25] [26]。TNF-a 和 IL-6 的增加会导致肝细胞损伤，然后，受损的肝细胞将释放白细胞介素-33 (IL-33)，该 IL-33 可以促进心脏促纤维化[27] [28]。而且，促炎细胞因子的持续产生增加了血管内皮上粘附分子的表达，这增加了发生动脉粥样硬化的风险，从而导致缺血性心肌病的发生[29]。研究表明，采取拮抗促炎细胞因子作用的治疗可改善肝脏脂肪变性、肝脏炎症和纤维化[30] [31]。无论是从理论还是临床实践都表明 MAFLD 患者的循环炎症与 CVD 相关联。

2.2. 氧化应激

氧化应激越来越被认为是包括代谢综合征在内的各种疾病过程的关键机制；代谢综合征可导致线粒体功能障碍，从而导致 ROS 生成过多和细胞损伤；ROS 的过量产生超过了细胞的抗氧化防御，导致细胞大分子的损伤，并影响细胞功能和生存能力，这也被称为氧化应激[32] [33]。其是多种肝病，如酒精性肝病[34]、MAFLD [35]、慢性病毒性肝炎和胆汁淤积性疾病的慢性肝损伤的关键致病因素，这种损伤最终会导致肝硬化。氧化应激增加可能通过诱导内皮功能障碍导致低级别炎症，进而增加血小板活化和血管斑块形成，从而促进 MAFLD 患者的 CVD 发展[18] [36]。

2.3. 胰岛素抵抗

肝脏与外周组织(如骨骼肌和脂肪组织)协调，是介导 IR 的中心器官。IR 一方面增加高血糖，引发氧化应激，增加低度炎症，并可能通过释放多种促动脉粥样硬化、促凝和促炎症介质导致内皮功能障碍[37]；另一方面加速了新的脂肪生成和甘油异生，促进了肝脏脂质的积累，从而进一步导致肝脏脂肪变性和 IR 的恶化，受损的 IR 诱导的高血糖和糖毒性导致了晚期糖基化终产物(AGEs)的过度产生[38]；AGEs 与特异性受体结合并刺激心脏和血管组织中的丝裂原活化蛋白激酶(MAPK)和非受体型酪氨酸蛋白激酶(Janus 激酶)信号传导，促进心脏纤维化和左心室舒张功能障碍；此外，IR 增加了线粒体对心脏中脂肪酸的摄取和 β-氧化，这通过损害增殖物激活受体 γ 共激活因子-1α/AMP 激活的蛋白激酶信号传导而导致线粒体功能障碍，并诱导活性氧(ROS)的产生，亦能诱导心脏纤维化和舒张功能障碍[39]。

2.4. 糖脂代谢

MAFLD 血脂异常典型特征是高水平的甘油三酯和极低密度脂蛋白(VLDL)残留脂蛋白，以及低水平的高密度脂蛋白胆固醇，易导致动脉粥样硬化[40]。动脉粥样硬化亦与高浓度的载脂蛋白 B (APOB)有关；为减少饮食中的胆固醇毒性，MAFLD 患者身体在通过增加肝脏产生非高密度脂蛋白胆固醇的过程中形成 APOB [41]。有研究发现，经活检证实的 MAFLD 患者中发现了与射血分数保留性心衰(HFpEF)相关的血清代谢产物，多种脂质代谢产物水平增加；脂质代谢也可能是连接 HFpEF 和 NAFLD 的重要途径[42]。

此外，膨胀的脂肪组织是促炎介质的重要来源，因为在人类中，每公斤多余的脂肪中估计会积累超

过 2000 万至 3000 万的巨噬细胞，而脂肪组织缺氧对抗炎细胞因子的产生有负面影响[43] [44]。脂肪组织还可分泌许多类似激素的分子，称为脂肪因子(如瘦素等)，参与身体的生理调节，脂肪因子与 MAFLD 有密切关系；MAFLD 患者的瘦素水平显著升高，循环瘦素水平越高，MAFLD 的严重程度越高，循环瘦素水平升高也会导致心脏肥大和内皮功能障碍[45]。脂肪组织炎症会亦导致全身炎症，从而促进 IR 和 CVD，并可能导致 MAFLD 恶化[46] [47]。

2.5. RAAS、SNS

肝脏中血管紧张素-II (AngII)水平升高与血管紧张素转换酶(ACE)2/Ang-(1-7)/Mas 受体失衡，以及肾上腺素能 β 受体过表达的可诱导肝脏 ROS 过量产生、脂质积聚和炎症；此外，代谢紊乱期间肝脏 ACE/AngII/Ang II 1 型受体(AT1R)途径的激活和儿茶酚胺浓度的增加通过激活肝星状细胞直接加剧肝纤维化[48]。并且，ACE/AngII/AT1R 能增加细胞内 Ca2 水平，并通过心肌细胞中的 G 蛋白 Gq/11 激活磷脂肌醇信号通路，从而刺激 MAPK、Janus 激酶/信号转导子和转录激活因子以及 PKC/NF-κB 信号传导[49]；这些信号通路通过刺激转录因子 c-Jun、c-Fos 和 Elk1 进一步促进心脏重塑[50]。

持续的 SNS 激活通过刺激兴奋性 G 蛋白的功能解耦联和 β-肾上腺素能受体的脱敏来诱导心脏重塑。激活的 SNS 导致免疫细胞浸润和心脏炎症反应，从而促进心脏纤维化[51]。一项来自 The Cooperative Health Research in South Tyrol (CHRIS)-NAFLD substudy 的研究(包括 356 人)也证实了，无论是否存在 T2DM 和其他心脏代谢风险因素，MAFLD (超声诊断)与心脏交感神经/副交感神经平衡受损之间的强烈关联[52]。以上证据表明，RAAS 和 SNS 的激活会导致代谢性疾病，并与心脏重塑有关。

2.6. 遗传多态性

一些与 MAFLD 相关的共享遗传多态性可能有助于 CVD 的发展。比如，PGC-1alpha Gly482Ser 多态性可能通过调节线粒体功能和生物发生、葡萄糖和脂质代谢而导致 MAFLD，其也通过增加 I 型胶原的合成代谢而参与心室肥大[53]。miR-21 通过增加脂肪生成和减少 VLDL 分泌来诱导肝脏脂质积聚，并通过抑制过氧化物酶增殖激活的受体-α 来刺激肝脏炎症和纤维化从而促进 MAFLD 的发展[54]；通过抑制 Sprouty-1 和 Sprouty-2，上调 MAPK 信号传导，增加循环 miR-21 水平有助于心脏重塑[55]。有学者指出，MAFLD 和 CHD 中也存在许多遗传因素共存[56]。到目前为止，由于缺乏广泛的基因暴露数据集，对 NAFLD 和 CVD 之间关系的孟德尔随机化(MR)研究的性能受到限制；在一项 MR 研究中研究者观察到，在排除了与 VLDL 分泌受损有关的遗传变异后，遗传预测的 MAFLD 与 CHD 之间存在着强有力的关联[57]。然而，这项研究受到 NAFLD 易感性基因数量相对较少(n = 12)的限制，更重要的是，缺乏基因暴露数据集；因此，不可能进行正式的 MR 分析，也不可能就 NAFLD 和 CHD 之间的关系强度(以及临床相关性)得出结论。而且 2 个遗传多态性基因型(PNPLA3 rs738409-I148M 和 TM6SF2 rss58542926-e167k)可能改变 NAFLD 与 CHD 风险之间的关联强度。尽管这两种基因型都增加了 NAFLD 患者发生更严重肝脏疾病的风险，但这两种基因型也都降低了血浆 VLDL 浓度，从而潜在地减弱了 NAFLD 与 CHD 风险之间的相关性[11]。在另一项 MR 研究中，该研究仅支持了 NAFLD 对动脉硬化的因果影响，然而，该研究没有发现 NAFLD 与 HF、CHD 和任何中风亚型的因果关系[58]。

2.7. 肠道菌群

MAFLD 与肠道细菌功能障碍和微生物衍生代谢物改变有关[22] [59]。肠道细菌功能障碍和代谢产物改变可能有助于病原体相关分子模式的产生，增加粘膜屏障通透性和受损的粘膜屏障通透性，导致系统性低级别炎症、IR 和肥胖，从而促进 MAFLD 的进展和 CVD 的发展[60] [61]。例如，三甲胺因肠道通透

性的增加能够进入循环系统，在循环系统中，三甲胺被含有肝黄素的单加氧酶 3 氧化为三甲胺 N-氧化物(TMAO)，TMAO 激活心肌细胞中的 TGFβ1/Smad2 和 p65 NF-κB 信号通路，促进心脏重塑；此外，TMAO 还通过影响心肌细胞的线粒体功能和细胞内钙处理来促进心脏重塑，并通过抑制内皮细胞中的 Sirtuin3-SOD2-mtROS 信号传导来诱导血管内皮损伤[62]。此外，肠道微生物代谢产物脂多糖溢出到循环中会在循环系统中产生广泛的炎症，从而增加动脉粥样硬化及其相关心脏重塑的风险[22]。不依赖于 MAFLD 的肠道菌群也能影响 CVD 的发生发展[63]。Loomba 等人为粪便微生物组衍生的宏基因组标记检测 NAFLD 晚期纤维化提供了有趣的证据；特别是大肠杆菌和变形杆菌的数量有所增加。这两种细菌都是革兰氏阴性菌，可通过增加门静脉和体循环中的脂多糖浓度诱导全身/肝脏炎症[64]；进而可能促进 CVD 的发展。

3. 总结

越来越多的证据表明，MAFLD 可能是心脏重塑进而导致 CVD 的关键驱动因素。然而，这种潜在联系没有得到充分的认识和重视。结合先前研究推测，MAFLD 与心脏重塑之间涉及大量复杂的机制，相互作用直接机制仍有待阐明。而且，许多相关临床研究支持 CVD 风险增加与 MAFLD 呈正相关，而由于肝活检采样有限，两者的相关性在大型人群中尚不明确。因此，在未来的研究中需要进一步探索 MAFLD 与 CVD 之间的因果关系。

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