心肝共治：代谢相关脂肪性肝病合并心血管疾病风险的协同管理

韦艺轩, 周晓东, 郑明华 [温州医科大学附属第一医院 感染内科（浙江省慢性肝病重症化精准诊治与转化重点实验室），浙江 温州 325000]

摘要：代谢相关脂肪性肝病（metabolic dysfunction-associated steatotic liver disease，MASLD）已成为全球最常见的慢性肝病，其发病率与肥胖、2型糖尿病、高血压等心脏代谢危险因素密切相关。近年来大量研究表明，MASLD的危害并非局限于肝脏本身，还与心血管疾病（cardiovascular disease，CVD）存在显著联系，二者在病理生理机制上共享多条路径，包括慢性低度炎症、胰岛素抵抗、内皮功能障碍和氧化应激等。MASLD患者罹患动脉粥样硬化、冠心病，心力衰竭和心律失常的风险显著升高；与此同时，CVD亦可通过影响共同代谢机制、交感神经系统和血流动力学进一步加重肝脏炎症与纤维化的进展。因此，MASLD与CVD并非彼此独立，心肝间的密切关联构成了重要的临床课题。尽管MASLD与CVD具有高度交叉的病理基础与临床风险，在当前临床实践中，脂肪性肝病患者的管理在肝病科与心血管科往往缺乏系统合作，导致MASLD患者早期筛查不足，治疗路径碎片化。本综述聚焦于MASLD与CVD间的双向关联，梳理其共同的发病机制与相互影响的临床证据，强调代谢综合管理的重要性，并提出通过生活方式干预和危险因素控制（如体质量、血糖、血脂）改善疾病结局的策略。未来应推动基于MASLD视角的CVD风险识别与管理模式，为代谢相关慢性疾病的综合防控提供新路径。

关键词：代谢相关脂肪性肝病；心血管疾病；心肝共同治疗

Heart and liver co-management: integrated management of metabolic dysfunction-associated steatotic liver disease with cardiovascular disease

Wei Yixuan, Zhou Xiaodong, Zheng Minghua *[Department of Infectious Diseases, The First Affiliated Hospital of Wenzhou Medical University (Key Laboratory of Diagnosis and Treatment for the Development of Chronic Liver Disease in Zhejiang Province), Zhejiang Wenzhou 325000, China]*

Abstract: Metabolic dysfunction-associated steatotic liver disease (MASLD) has emerged as the most prevalent chronic liver disease globally, with its incidence closely linked to cardiometabolic risk factors such as obesity, type 2 diabetes and hypertension. Recent extensive research revealed that the impact of MASLD extended beyond liver itself, demonstrating significant bidirectional associations with cardiovascular disease (CVD). These conditions shared multiple intertwined pathophysiological pathways, including chronic low-grade inflammation, insulin resistance, endothelial dysfunction and oxidative stress. Patients with MASLD exhibited a markedly elevated risk of developing atherosclerosis, coronary heart disease, heart failure and arrhythmias. Conversely, CVD could further exacerbate hepatic inflammation and fibrosis progression by disrupting shared metabolic mechanisms, activating the sympathetic nervous system, and altering hemodynamics. Thus, MASLD and CVD were not mutually exclusive but interconnected, presenting a significant clinical challenge. Despite the highly overlapping pathological foundations and clinical risks between MASLD and CVD, current clinical practice often lacked systematic collaboration between hepatology and cardiology departments. This fragmentation resulted in inadequate early screening

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通信作者：郑明华 Email: zhengmh@wmu.edu.cn

for MASLD patients and disjointed treatment pathways. This review focused on the bidirectional relationship between MASLD and CVD, delineated their shared pathogenic mechanisms and clinical evidence of mutual influence, and underscored the imperative for integrated metabolic management. We proposed strategies centered on lifestyle interventions and rigorous control of metabolic risk factors (e.g., weight, blood glucose, lipids) to improve disease outcomes. Moving forward, it was essential to advance CVD risk identification and management models from an MASLD perspective, offering novel paradigms for the comprehensive prevention and control of metabolism-related chronic diseases.

Keywords: Metabolic dysfunction-associated steatotic liver disease; Cardiovascular disease; Heart and liver co-management

随着全球肥胖和糖尿病发病率的持续上升，代谢相关脂肪性肝病（metabolic dysfunction-associated steatotic liver disease，MASLD）已成为慢性肝病的主要原因之一，影响全球约30%的成年人口，给公共卫生带来严峻挑战，并对患者和医疗体系造成了沉重的经济负担[1]。MASLD是对原“非酒精性脂肪性肝病（non-alcoholic fatty liver disease，NAFLD）”诊断概念的更新，其诊断依据为：存在影像学或组织学明确的肝脏脂肪变性，在排除显著饮酒（女性≥ 20 g/d，男性≥ 30 g/d）及其他特定肝病（如病毒性肝炎、药物性肝病等）后，同时合并至少1种代谢危险因素，包括2型糖尿病、肥胖、高血压、血脂异常或胰岛素抵抗等[2]。MASLD术语的引入反映了从“排他性定义”向“代谢驱动性理解”的转变，强化了其以代谢紊乱为核心病因的概念，有助于提升临床识别率、减少诊断污名化，并推动研究与治疗策略的标准化[3]。

MASLD是一种具有进展性的慢性肝病，其自然病程可从单纯性脂肪变性逐步演变为代谢功能障碍相关的脂肪性肝炎（metabolic dysfunction-associated steatohepatitis，MASH）、进一步发展为显著肝纤维化、肝硬化甚至肝细胞癌（hepatocellular carcinoma，HCC）[4]。然而MASLD的危害远不止肝脏本身，近年的研究一致指出其具有系统性代谢紊乱的本质，常伴心脑血管疾病、微血管病变、慢性肾脏病及肌肉减少症等多系统并发症[5,6]。其中，心血管疾病（cardiovascular disease，CVD）是MASLD最常见的肝外并发症之一，也是MASLD相关全因死亡的首要原因。已有大量研究证实，MASLD本身即为CVD的独立危险因素，而不仅仅通过共享代谢风险因素产生间接关联[5,7,8]。尽管MASLD的系统性特征日益明确，多学科协作管理仍面临结构性滞后。目前，MASLD与2型糖尿病的共病识别和干预已在多国指南中建立了较为完善的路径，推动了内分泌与肝病专科间的协作实践[9]。相较之下，MASLD与CVD虽关系密切，但在临床实际中，肝病科与心血管科间的信息交流和协同诊疗仍相对不足，缺乏系统整合成为影响患者长期预后管理的重要障碍。因此，从MASLD视角重新审视心血管及肝脏的风险识别、干预契机及整合式管理模式，是当前MASLD管理的关键议题之一。

1 心肝协同管理的循证依据及病理机制

1.1 MASLD与CVD风险增加的相关证据 过去10年间，大量前瞻性队列研究和荟萃分析系统揭示了MASLD与CVD风险升高间的紧密关联[10-13]。最新数据显示，MASLD患者在合并肝纤维化时，面临更高的动脉粥样硬化性心血管疾病（atherosclerotic cardiovascular disease，ASCVD）风险[14-16]。一项纳入36项队列研究（总样本量约580万中年受试者，随访中位时间6.5年）的荟萃分析显示：即使校正年龄、性别、体重指数、糖尿病等传统心脏代谢危险因素后，MASLD仍显著增加长期致死/非致死性CVD事件风险（*HR*=1.45，95%*CI*：1.31～1.61）[17]。另一项基于瑞典全国注册数据的长期队列研究（1966年至2016年，10 422例）在中位13.6年随访期间，发现经组织学确诊的MASLD患者与匹配对照组（46 517例）相比，其主要不良心血管事件（major adverse cardiovascular events，MACE）的风险显著增高（24.3例/1000人年比16.0例/1000人年；*HR* = 1.63，95%*CI*：1.56～1.70）。MACE的发生率随着MASLD严重程度的增加而逐步增加（*P* = 0.02），其中肝硬化患者发生率最高（差异值：27.2例/1000人年；*HR* = 2.15，95%*CI*：1.77～2.61）[18]。美国心脏协会（American Heart Association，AHA）2022年声明也将MASLD列为ASCVD的明确危险因素[19]。

除ASCVD外，MASLD还与心力衰竭、心律失常等其他CVD密切相关[20,21]。心力衰竭是MASLD患者中值得关注的心血管并发症。MASLD通过多种机制参与心力衰竭的发生和进展，包括系统性慢性炎症、胰岛素抵抗、心肌脂毒性、内皮功能

障碍和氧化应激等，最终导致心肌结构与功能重构。近期一项涵盖11项队列研究、约1120万受试者的荟萃分析表明，MASLD显著增加新发心力衰竭风险（*HR* = 1.50，95%*CI*：1.34～1.67），且该相关性在校正2型糖尿病、高血压等危险因素后依然成立[22]。在心力衰竭的不同表型中，射血分数保留的心力衰竭（heart failure with preserved ejection fraction，HFpEF）尤为受到关注。目前HFpEF被认为是一种以心肌舒张功能障碍和心室顺应性下降为特征的临床综合征，具有典型的代谢炎症背景[23]。MASLD与HFpEF在病理生理机制上高度重叠，两者均存在内皮功能障碍、微血管稀疏、心肌能量代谢紊乱及心肌间质轻度纤维化等改变。

此外，MASLD还与多种心律失常（尤其是心房颤动）的发生密切相关。相关机制包括心房结构重构、脂肪浸润、自主神经功能紊乱及慢性低度炎症状态[24]。一项纳入16项回顾性队列研究（包括约1950万受试者，中位随访时间7.2年）的荟萃分析发现，MASLD患者发生新发房颤的风险显著升高（*HR* = 1.20，95%*CI*：1.10～1.32），该关联在多变量调整后依旧稳健[25]。MASLD还被观察到与瓣膜钙化等其他心脏瓣膜结构异常有关[20]。

1.2 心肝交互的病理生理机制 MASLD和CVD在病理生理机制上存在密切关联，且呈复杂的双向作用。二者共享多种核心机制，如胰岛素抵抗、低度慢性炎症和氧化应激与内皮功能障碍，且在疾病进展过程中形成双向促进作用[17,26-28]。MASLD可通过一系列代谢紊乱机制增加CVD风险：肝脏产生过量的活性氧（reactive oxygen species，ROS），诱发脂质过氧化并激活肝星状细胞，进而引起肝脏炎症和纤维化[29]；过量的ROS还可诱导低密度脂蛋白（low-density lipoprotein，LDL）氧化，促进巨噬细胞转化为泡沫细胞，是动脉粥样硬化病变形成和进展的关键环节[30]。此外，胰岛素抵抗作为MASLD的核心病理基础之一，不仅促进肝脏脂肪生成，还以多种方式影响全身微血管和大血管稳态，加速动脉粥样硬化进展[31]。慢性高血糖进一步损伤血管内皮、刺激平滑肌细胞增殖、提高血小板活性并诱导ROS产生，从多通路加剧血管病变[32]。低度炎症亦通过加剧内皮功能障碍、改变血管张力和促进血管斑块形成参与CVD病理过程[33]。血管炎症、脂质沉积、血管重塑、内皮损伤和高凝状态等机制恶性循环，从而导致动脉粥样硬化和心肌炎症，促进CVD的进展。随着疾病进展，MASLD可能发展为肝硬化，后者可引发肝硬化性心肌病，其表现为基础无心脏疾病的肝硬化患者出现心功能不全，主要特征为对刺激的收缩反应性下降和（或）舒张功能障碍，并伴有电生理异常[34]。肝硬化通过多重病理机制损害心脏功能：门静脉高压导致的高动力循环状态使心脏代偿性增加心率和每搏输出量，引发心肌肥厚；炎症因子（如肿瘤坏死因子-α、白细胞介素-6）及胆汁酸沉积直接损伤心肌，诱导心肌间质纤维化和细胞肥大；细菌移位产生内毒素，激活系统性炎症反应。上述诸多因素最终导致心肌结构重塑，如左心房扩大、心室肥厚等，进而演变为心力衰竭并增加心血管死亡风险[35]。

CVD也可能反向加剧MASLD的肝脏病理进程。研究表明，心肌梗死可加速MASLD患者的肝脂肪沉积、纤维化进展和肝细胞异常增殖，可能与循环中Ly6C^{hi}单核细胞增加并迁移至肝组织有关。同时，心肌梗死显著增加血液循环和心脏局部的成骨蛋白（periostin）水平，后者可直接作用于肝细胞与星状细胞，诱导肝脂肪沉积和纤维化。这些临床前和临床结果提示心肌梗死可通过系统炎症和促纤维化因子扰乱肝脏稳态，加速MASLD肝脏病理进展[36]。心力衰竭同样可通过多重病理生理机制引起肝脏损伤。心力衰竭患者心排血量下降致肝脏灌注不足，引起肝细胞代谢应激、变性与坏死；静脉压升高导致肝静脉回流受阻，形成肝窦淤血（即淤血性肝病）；同时激活肾素-血管紧张素-醛固酮系统（renin angiotensin aldosterone system，RAAS），造成水钠潴留，进一步加重肝脏淤血。肝窦淤血叠加低度炎症激活肝星状细胞，促进胶原沉积及纤维化发展，最终可能演变为心源性肝硬化[37,38]。

综上所述，MASLD与CVD间存在显著的双向病理交互作用：肝脏病变显著增加心血管风险，CVD亦可反向加重肝脏损伤。这种复杂的交互机制提示，仅关注单一器官已无法有效防治相关疾病。临床管理需从“心肝共治”的视角出发，加强跨学科协作，开展系统性风险评估与综合干预。随着对代谢性疾病在心脏与肝脏系统间相互作用机制认知的不断加深，预防医学正面临跨学科融合的迫切需求：一方面，预防性心脏病学强调控制传统心血管风险因素；另一方面，新兴的预防性肝病学通过早期筛查及生活方式干预阻断MASLD进展。二者协同形成统一防线，以降低心肝共病的发病率与死亡率[39]。

2 心肝共同管理的现实挑战

2.1 临床实践困境 尽管MASLD和CVD密切相关，但在我国临床实践中，这一关联仍常被忽视。尤其是肝酶正常或仅轻度升高、缺乏明显症状的肝纤维化患者，往往不会就诊于肝病专科，而是由非肝病专业医生（如心内科、内分泌科或基层医疗人员）进行初始管

理。因此，在临床实践中可能面临以下几方面挑战。

第一，在诊疗过程中，肝脏风险评估常被置于次要地位。因心血管事件的急迫性，心血管治疗优先，往往导致肝病监测和干预被延迟或遗漏。第二，MASLD慢性进展且没有明显临床症状，在时间有限的诊疗中可能不会立即进行筛查，医生往往优先处理急性或症状明显的问题，MASLD早期筛查可能因此被忽略。第三，当前临床常用的肝功能检测或腹部超声、计算机体层成像等影像学检查对早期肝纤维化识别能力有限，且缺乏统一、标准化的筛查路径，从而延误了对高危患者的识别与干预。第四，目前尽管多项糖尿病管理指南（如美国糖尿病学会和欧洲糖尿病研究协会）已明确建议对2型糖尿病患者进行肝脏纤维化风险评估，并在适当情况下采用非侵入性工具 [如肝脏瞬时弹性成像、肝纤维化4因子指数（fibrosis index based on the 4 factors，FIB-4）] 进行筛查[2,40]，但多数心血管疾病管理指南（包括高血压、心力衰竭及冠心病等领域的权威指南）尚未将MASLD或肝纤维化纳入常规评估范围。这一差异导致在以CVD为主诉的临床路径中，脂肪性肝病相关风险因素未获足够重视，从而影响对高危患者的早期识别与干预，客观上降低了非肝病医生的筛查主动性[3]。

2.2 药物临床试验困境 MASLD作为一种以代谢紊乱为核心的系统性疾病，其治疗策略大多集中在改善代谢环境及肝脏病理过程。然而，肝病与心血管领域的交叉研究与协作仍较为有限，疾病的早期识别与联合治疗明显滞后。目前对MASLD发病机制的理解虽日益深入，但多数治疗策略主要关注肝脏结局，对其潜在的心血管获益缺乏系统性研究。同样，心血管风险管理也少有将肝脏因素纳入考虑范围，导致MASLD患者在治疗过程中存在“管理盲区”。这种缺口在临床试验设计中尤为突出。一方面，MASLD相关研究多聚焦于肝脂肪变性、气球样变、肝纤维化等组织学终点，而较少将评估心血管事件作为主要或次要结局指标[41,42]；另一方面，CVD领域的试验则通常忽略肝脏特异性评估指标[43,44]。这种单一取向导致研究数据的异质性上升，不仅影响结果的可比性，也限制了整合性治疗策略的形成[45]。此外，为全面评估心肝联合效应，临床试验往往需要扩大入组人群的范围，并设计涵盖肝脏和心血管多维度结局的复合终点，这就显著增加了研究的复杂性和流程难度，延长随访周期，推高成本投入。同时，跨学科的试验框架和标准化评价体系尚未成熟，这限制了大型、多中心心肝联合干预研究的开展和推广，进而影响了MASLD及其相关心血管并发症综合治疗药物的研发。

3 MASLD 与 CVD 的双向筛查

3.1 CVD患者肝纤维化筛查的必要性 CVD患者是MASLD进展成肝硬化乃至发生肝脏相关事件的高危人群，对确诊CVD的患者进行早期肝脏健康评估至关重要。然而，当前CVD相关指南尚未建议常规筛查MASLD[19,46]。因此，在推荐MASLD筛查前，应证实常规筛查能以经济的方式同步改善肝脏和心血管结局[47]。

肝组织活检是肝纤维化病理分期的金标准，但其为有创检查，存在取样误差、观察者间变异性及成本较高等局限[48]。此外，并发症风险除了常规出血、感染外，因CVD人群普遍使用抗凝药物或抗血小板药物而使出血风险进一步增高。这些局限性促使在临床中优先选择非侵入性检查（noninvasive tests，NITs）对肝纤维化进行初步筛查。NITs不仅可减少肝组织活检需求，还有助于识别CVD高风险患者。非肝病专科医生应结合NITs，如肝脏瞬时弹性成像（FibroScan®）或血清生物标志物/评分（如FIB-4），评估高危患者的肝纤维化程度[49,50]。FIB-4是一种经济高效的筛查工具，尤其适用于2型糖尿病、CVD、慢性肾病及具有其他心脏代谢风险因素的患者，其在排除晚期肝纤维化方面具有良好的特异性和阴性预测价值；FIB-4动态变化有助于预测肝纤维化进展，为评估长期肝脏相关事件及死亡风险提供个体化分层依据[50,51]。FibroScan®是一种基于超声的无创技术，通过肝硬度值评估肝纤维化程度，并通过受控衰减参数量化肝脏脂肪变性[52]。经济效益分析对推动肝纤维化筛查纳入常规诊疗体系至关重要，但其结果易受多种因素影响[53]。目前大多数分析集中在已确诊MASLD的患者[54]或存在肥胖2型糖尿病、代谢综合征等高风险因素的人群[55,56]，未来研究需重点探索在CVD患者中评估无创检测流程的成本效益、采用更保守的疾病进展模型以及整合Resmetirom等新疗法的影响等方面[53]。

目前，针对肥胖、2型糖尿病或代谢综合征高危人群，许多学科指南已推荐进行MASLD筛查。亚太肝病学会、美国肝病研究学会和美国糖尿病学会均强调对合并肝纤维化的MASLD患者（尤其是2型糖尿病或肥胖个体）实施病例筛查策略[2,40,48,57]。欧洲肝病学会、糖尿病学会及肥胖学会联合发布的最新临床实践指南强烈推荐采用分步筛查策略：首选FIB-4进行初筛，对结果异常者进一步采用FibroScan®等影像学技术确认或排除晚期肝纤维化[2]。

3.3 MASLD患者的心血管风险评估 鉴于MASLD与CVD的密切联系，相关共识及临床指南已明确

将CVD筛查纳入MASLD患者的综合管理[2,48,58]。亚太肝病学会在其关于MASLD诊断和管理的临床实践指南中强烈推荐对MASLD患者进行CVD风险评估。该指南亦强调，需识别并妥善治疗合并的血脂异常、高血压及糖尿病，以最大程度降低肾脏、心血管及其他器官系统的疾病风险[48]。美国肝病研究学会、美国糖尿病学会及欧洲肝病学会、糖尿病学会及肥胖学会联合指南均强烈建议临床医生应评估成年MASLD患者的心血管风险[2]。由国际多学科专家通过改良德尔菲方法达成的共识意见进一步指出，无论是否存在动脉粥样硬化的危险因素，所有MASLD患者均应进行CVD筛查。

4 “心肝共治”管理策略 — 生活方式干预

生活方式干预是管理MASLD及相关CVD风险的基础，涵盖低热量饮食、规律运动和体重控制，是所有患者的首选方案[59,60]。

体重管理尤为重要，对于肥胖患者，长期显著减重可带来心肝双重益处[61]。研究表明，5%～10%的适度减重则有助于减轻肝脏脂肪变性和炎症，显著降低心血管风险，而体质量下降10%以上能有效改善MASH及肝纤维化的组织学表现[62]。基于这一证据，当前的MASLD管理指南建议超重或肥胖患者应减轻5%～10%的体质量[48]。对于病态肥胖患者，减重手术是MASLD的有效治疗手段，包括袖状胃切除术、Roux-en-Y胃旁路术、可调节胃束带术及胆胰分流术等[48]。这些治疗手段可实现高达30%的持续减重效果，同时能改善代谢功能障碍，减少CVD的不良临床结局，并减少总体死亡率[63]。此外，有证据表明，慢性心力衰竭合并病态肥胖患者接受减重手术可提升心脏移植成功率[64]，在某些情况下甚至可能避免移植需求[65,66]。

运动作为重要干预措施，推荐每周累计至少150 min中等强度有氧运动或75 min高强度有氧运动，能够改善肝脏脂肪沉积并降低CVD风险[67,68]。值得注意的是，降低CVD风险的获益可能没有运动量的最低阈值，即使未达到推荐运动量，适量增加身体活动同样有益[69]。因此，对无法达到最低运动要求的成人而言，进行少量中高强度运动也有助于降低CVD风险[68,69]。

饮食调整则通过低热量摄入促进体质量减轻，并改善肝酶水平、脂肪变性及炎症状态[70-72]。2025年亚太肝病学会指南建议MASLD患者每日摄入5023～7534 kJ热量，或每日减少2093～3139 kJ以实现减重目标[48]。地中海饮食模式因其降低精制碳水和加工食品摄入、增加单不饱和脂肪酸与ω-3脂肪酸摄入的特征，被广泛认可为对MASLD和CVD均有益的科学饮食模式[57,73]。研究显示，该饮食不仅可改善肝脏脂肪沉积和胰岛素抵抗，还能降低肝癌及心血管事件风险[74-76]。

5 “心肝共治”相关药物

尽管目前对MASLD与CVD的病理机制认识已取得显著进展，但现有治疗对肝脏及心血管结局的长期获益仍认知不足。这一认知差距反映在当前的治疗策略中：MASLD治疗主要关注改善肝脏病变，但对长期心血管结局的考量和相关证据仍较有限；相应地，心血管疾病的治疗通常较少关注其对肝脏的潜在益处。以下将从三大核心药物治疗策略：代谢靶向治疗、肝脏靶向治疗和心血管靶向治疗概述当前药物治疗的现状，并探讨具有“心肝共治”潜力的药物。

5.1 代谢靶向治疗：心肝共管的基础

鉴于MASLD和CVD存在共同的代谢起源，针对其共同病理机制的药物干预有望同步减少肝脏和心血管并发症。其干预策略一方面是在超重和代偿性肝-心疾病的患者中实现负能量平衡，过量的脂肪积聚会导致肝脏脂肪变性，进而可进展为MASH和纤维化。同时，释放的脂质在心脏的异常沉积亦会增加心血管风险[77]。因此，通过促进脂肪酸氧化、提高代谢率、减少热量摄入及通过下丘脑途径调节食欲来减轻肝脏和心脏的代谢负荷至关重要。另一方面是靶向MASLD与CVD共有的关键代谢通路。例如，胰高血糖素样肽-1（glucagon-like peptide-1，GLP-1）受体激动剂和其他多受体促凝剂，包括双重GLP-1受体和葡萄糖依赖性促胰岛素肽受体（glucose-dependent insulinotropic polypeptide receptor，GIPR）激动剂、GLP-1受体和胰高血糖素受体（glucagon receptor，GCGR）激动剂，以及三重GLP-1受体/GIPR/GCGR激动剂，已成为治疗MASLD/MASH及降低相关心血管风险的极具前景的药物[78-80]。此类药物在改善胰岛素敏感性、减少肝脏脂肪积聚和全身减重方面效果显著[81,82]。在GLP-1受体激动剂中，司美格鲁肽为MASLD/MASH的治疗提供了有力的循证证据[83]。其Ⅲ期随机安慰剂对照试验ESSENCE（NCT04822181）结果显示，MASH合并肝纤维化（F2/F3期）患者接受司美格鲁肽（2.4 mg/周）治疗72周后，有62.9%患者实现MASH消退，而安慰剂组为34.3%。此外，司美格鲁肽组实现肝纤维化至少1级改善的患者比例也显著升高（36.8%比22.4%，$P < 0.001$）[84]。GLP-1受体/GIPR双重激动剂Tirzepatide的Ⅱ期安慰剂对照试验SYNERGY-NASH（NCT04166773）也得到积极结果，其不同剂量治疗组MASH缓解率（43.6%、

55.5%和62.4%）均显著优于安慰剂组（9.8%）[85]。

除显著改善肝脏代谢损伤外，这类药物还具有明确的心血管保护作用。SUSTAIN 6试验（NCT01720446）证实，司美格鲁肽使2型糖尿病高危患者MACE风险降低26%，这主要归因于非致死性卒中风险下降39%[86]。SELECT（NCT 03574597）试验进一步在确诊CVD的超重或肥胖个体中证实，司美格鲁肽可使MACE风险降低20%（*HR* = 0.80，95%*CI*：0.72～0.90）[87]。基于其获益证据，GLP-1受体激动剂已被纳入多项CVD高危患者的管理指南[88]，为MASLD与CVD的共治提供了重要的药物选择。尽管基于肠促胰岛素的药物疗效显著，其临床应用仍面临高成本和可及性等挑战。未来研究需进一步探索其在肝纤维化高风险的非糖尿病人群中的疗效与安全性。

5.2 肝脏靶向治疗：优化肝脏获益与规避心血管风险 相较于系统性代谢调节药物，肝脏靶向治疗更侧重于直接干预MASH和肝纤维化的病理进程[89]。然而此类疗法在CVD共病患者中的应用仍需谨慎，尤其需关注潜在的药物相互作用和心血管不良反应风险[90,91]。例如，选择性甲状腺激素受体（thyroid hormone receptor，THR）-β激动剂Resmetirom在Ⅲ期MAESTRO-NASH试验中已证实可显著改善肝纤维化，是首个获美国食品药品监督管理局批准的MASH治疗药物。但需注意该药与氯吡格雷、他汀类等常用CVD药物存在潜在相互作用，可能影响药物代谢或增加心血管事件风险[92]。

过氧化物酶体增殖物激活受体（peroxisome proliferator-activated receptor，PPAR）是调节脂质代谢、葡萄糖稳态和炎症的关键核受体。PPAR-γ激动剂噻唑烷二酮类药物（如吡格列酮）虽可改善胰岛素抵抗及肝脏组织学[93]，但存在体质量增加和水钠潴留的风险，故不适用于合并严重心力衰竭的患者[94]。双重PPAR-α/γ激动剂Saroglitazar在Ⅱ期试验（NCT03061721）中显示，Saroglitazar（4 mg/d）可降低肝脏脂肪含量并改善胰岛素抵抗[95]。该药已在印度获批用于治疗MASH，目前正于全球开展Ⅱb期试验[96]。Saroglitazar还可降低循环胆固醇、甘油三酯和低密度脂蛋白胆固醇（low-density lipoprotein cholestero，LDL-C）水平[97]。尽管如此，目前尚缺乏直接证据表明此类药物能降低CVD事件发生率。

其他肝脏靶向候选药物如法尼酯X受体（farnesoid X receptor，FXR）激动剂、乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）抑制剂、脂肪酸合成酶（fatty acid synthetase，FAS）抑制剂等，虽在改善肝脏组织学方面显示出疗效，但其心血管安全性仍存在不确定性，表现出差异化的风险谱[98-100]。FXR激动剂奥贝胆酸在3期REGENERATE试验（NCT04906421）中引发了血脂异常，表现为降低高密度脂蛋白胆固醇且增加LDL-C水平[99]。选择性ACC抑制剂PF-05221304在为期16周的Ⅱ期试验中显示出肝脏脂肪含量降低超过50%的疗效，然而50 mg/d剂量组中25%的患者出现了无症状的高甘油三酯血症，引发了对其潜在心血管风险的担忧[100]。

5.3 心血管靶向治疗：待验证的肝脏潜力 探索心血管药物在MASLD治疗中的潜力是当前研究的前沿方向之一。具有潜在治疗价值的药物包括他汀类药物、钠-葡萄糖共转运蛋白2抑制剂（sodium-glucose cotransporter 2 inhibitors，SGLT-2i）、阿司匹林以及RAAS抑制剂。

部分CVD一线用药，如他汀类药物[101]，因其具有抗炎、抗氧化及稳定斑块等多重效应，可能对MASLD产生直接或间接的益处[102]。研究表明，他汀类药物可延缓肝纤维化进展，降低全因死亡率、肝脏相关事件和HCC发生风险[103,104]。然而，目前他汀类药物在MASLD治疗中的应用旨在降低CVD风险，其对肝脏组织学改善的直接疗效尚未明确，需进一步研究验证其在MASLD管理中的独立治疗价值[102]。

SGLT-2i因其明确的心血管和肾脏保护作用，已被广泛用于2型糖尿病及高危CVD患者的管理。近年来，有研究显示SGLT-2i亦可改善肝脏脂肪含量和胰岛素抵抗，提示其可能具有一定的肝脏保护效应。然而其在改善MASLD/MASH组织学方面的高质量证据仍较有限，需进一步研究确认[105,106]。近期，首个以肝脏病理学改善为主要终点的多中心随机对照临床试验DEAN（NCT03723252）结果的发表填补了这一证据空白。该研究证实，SGLT-2i（达格列净10 mg/d）干预48周可有效改善MASH患者的肝脏病理结局，SGLT-2i组达到主要终点（MASH改善，定义为肝脏病理NAFLD活动性评分降低≥ 2分或总分≤ 3分，且纤维化无恶化）的患者比例显著高于安慰剂组（53%比30%，*RR* = 1.73，*P* = 0.006）；同时其MASH逆转率（23%比8%，*P* = 0.01）和纤维化改善率（45%比20%，*P* = 0.001）亦显著优于安慰剂组，其体质量、腰围、血压以及糖代谢和脂代谢指标等方面的改善程度也显著高于安慰剂组[107]。

其他潜力药物方面，一项概念验证随机临床试验（NCT04031729）表明，低剂量的阿司匹林（81 mg/d）可显著降低肝脏脂肪含量[108]。此外，血管紧张素转换酶抑制剂和血管紧张素Ⅱ受体阻滞剂在降血压及CVD风险管理中的地位已被确立，部分

动物和临床研究也观察到其具有一定的抗肝纤维化效应[109,110]。然而，这些药物对肝脏组织学改善的直接疗效尚缺乏系统性的临床证据支持，未来仍需进一步临床研究评估其在MASLD/MASH治疗中的潜在适应证。

6 总结

MASLD与CVD在流行病学、病理生理及临床表现上均呈现高度重叠与互动，其共病机制复杂，涉及炎症、代谢紊乱、氧化应激及器官交叉调节等多个层面。MASLD不仅局限于肝脏本身，更显著增加心血管事件的风险。单一器官管理已难以应对其复杂性，推动“心肝共治”成为临床管理的关键方向。通过多学科协作，统筹评估代谢状态、同步干预肝脏与心血管风险因素，才能有效控制疾病进展，提升整体健康水平，实现真正的精准治疗和长期获益。

利益冲突 所有作者声明不存在利益冲突

参考文献

[1] ZHANG H, ZHOU X D, SHAPIRO M D, et al. Global burden of metabolic diseases, 1990—2021[J]. Metabolism,2024,160:155999.

[2] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD)[J]. J Hepatol,2024,81(3):492-542.

[3] ZHOU X D, TARGHER G, BYRNE C D, et al. Metabolic dysfunction-associated fatty liver disease: bridging cardiology and hepatology[J]. Cardiology Plus,2024,9(4):275-282.

[4] ANSTEE Q M, TARGHER G, DAY C P. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis[J]. Nat Rev Gastroenterol Hepatol,2013,10(6):330-344.

[5] TARGHER G, TILG H, BYRNE C D. Non-alcoholic fatty liver disease: a multisystem disease requiring a multidisciplinary and holistic approach[J]. Lancet Gastroenterol Hepatol,2021,6(7):578-588.

[6] TARGHER G, BYRNE C D, TILG H. MASLD: a systemic metabolic disorder with cardiovascular and malignant complications[J]. Gut,2024,73(4):691-702.

[7] LEE H, LEE Y H, KIM S U, et al. Metabolic dysfunction-associated fatty liver disease and incident cardiovascular disease risk: a nationwide cohort study[J]. Clin Gastroenterol Hepatol,2021,19(10): 2138-2147.

[8] ZHOU X D, CAI J, TARGHER G, et al. Metabolic dysfunction-associated fatty liver disease and implications for cardiovascular risk and disease prevention[J]. Cardiovasc Diabetol,2022,21(1):270.

[9] CUSI K, ABDELMALEK M F, APOVIAN C M, et al. Metabolic dysfunction-associated steatotic liver disease (MASLD) in people with diabetes: the need for screening and early intervention. A consensus report of the American Diabetes Association[J]. Diabetes Care,2025,48(7):1057-1082.

[10] CAI J, ZHANG X J, JI Y X, et al. Nonalcoholic fatty liver disease pandemic fuels the upsurge in cardiovascular diseases[J]. Circ Res, 2020,126(5):679-704.

[11] BROUWERS M C G J, SIMONS N, STEHOUWER C D A, et al. Non-alcoholic fatty liver disease and cardiovascular disease: assessing the evidence for causality[J]. Diabetologia,2020,63(2):253-260.

[12] TARGHER G, BYRNE C D, LONARDO A, et al. Non-alcoholic fatty liver disease and risk of incident cardiovascular disease: a meta-analysis[J]. J Hepatol,2016,65(3):589-600.

[13] MUZUROVIĆ E, PENG C C, BELANGER M J, et al. Nonalcoholic fatty liver disease and cardiovascular disease: a review of shared cardiometabolic risk factors[J]. Hypertension,2022,79(7):1319-1326.

[14] ZHOU Y Y, ZHOU X D, WU S J, et al. Nonalcoholic fatty liver disease contributes to subclinical atherosclerosis: a systematic review and meta-analysis[J]. Hepatol Commun,2018,2(4):376-392.

[15] ZHOU Y Y, ZHOU X D, WU S J, et al. Synergistic increase in cardiovascular risk in diabetes mellitus with nonalcoholic fatty liver disease: a meta-analysis[J]. Eur J Gastroenterol Hepatol,2018,30(6): 631-636.

[16] CASTILLO-NÚÑEZ Y, ALMEDA-VALDES P, GONZáLEZ-GÁLVEZ G, et al. Metabolic dysfunction-associated steatotic liver disease and atherosclerosis[J]. Curr Diab Rep,2024,24(7):158-166.

[17] MANTOVANI A, CSERMELY A, PETRACCA G, et al. Non-alcoholic fatty liver disease and risk of fatal and non-fatal cardiovascular events: an updated systematic review and meta-analysis[J]. Lancet Gastroenterol Hepatol,2021,6(11):903-913.

[18] SIMON T G, ROELSTRAETE B, HAGSTRÖM H, et al. Non-alcoholic fatty liver disease and incident major adverse cardiovascular events: results from a nationwide histology cohort[J]. Gut,2022,71(9): 1867-1875.

[19] DUELL P B, WELTY F K, MILLER M, et al. Nonalcoholic fatty liver disease and cardiovascular risk: a scientific statement from the American Heart Association[J]. Arterioscler Thromb Vasc Biol,2022,42(6):e168-e185.

[20] ANSTEE Q M, MANTOVANI A, TILG H, et al. Risk of cardiomyopathy and cardiac arrhythmias in patients with nonalcoholic fatty liver disease[J]. Nat Rev Gastroenterol Hepatol,2018,15(7):425-439.

[21] TARGHER G, BYRNE C D, TILG H. NAFLD and increased risk of cardiovascular disease: clinical associations, pathophysiological mechanisms and pharmacological implications[J]. Gut,2020,69(9):1691-1705.

[22] MANTOVANI A, PETRACCA G, CSERMELY A, et al. Non-alcoholic fatty liver disease and risk of new-onset heart failure: an updated meta-analysis of about 11 million individuals[J]. Gut,2022:gutjnl-2022-327672.

[23] ZHOU X D, LIP G Y H, ZHENG M H. From HPpEF to “metabolic (dysfunction)-associated HPpEF”: time to act[J]. Sci Bull (Beijing),2024,69(7):850-852.

[24] CHEN Z, LIU J, ZHOU F, et al. Nonalcoholic fatty liver disease: an emerging driver of cardiac arrhythmia[J]. Circ Res,2021,128(11):1747-1765.

[25] MANTOVANI A, MORANDIN R, SANI E, et al. MASLD is associated with an increased long-term risk of atrial fibrillation: an updated systematic review and meta-analysis[J]. Liver Int,2025,45(1):e16128.

[26] ZHENG H, SECHI L A, NAVARESE E P, et al. Metabolic dysfunction-associated steatotic liver disease and cardiovascular risk: a comprehensive review[J]. Cardiovasc Diabetol,2024,23(1):346.

[27] ADAMS L A, ANSTEE Q M, TILG H, et al. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases[J]. Gut,2017,66(6):1138-1153.

[28] YKI-JÄRVINEN H. Non-alcoholic fatty liver disease as a cause and a consequence of metabolic syndrome[J]. Lancet Diabetes Endocrinol,2014,2(11):901-910.

[29] CHEN Z, TIAN R, SHE Z, et al. Role of oxidative stress in the pathogenesis of nonalcoholic fatty liver disease[J]. Free Radic Biol Med,2020,152:116-141.

[30] INCALZA M A, D’ORIA R, NATALICCHIO A, et al. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases[J]. Vascul Pharmacol,2018,100:1-19.

[31] SAKURAI Y, KUBOTA N, YAMAUCHI T, et al. Role of insulin resistance in MAFLD[J]. Int J Mol Sci,2021,22(8):4156.

[32] PASTERKAMP G. Methods of accelerated atherosclerosis in diabetic patients[J]. Heart,2013,99(10):743-749.

[33] STAHL E P, DHINDSA D S, LEE S K, et al. Nonalcoholic fatty liver disease and the heart: JACC state-of-the-art review[J]. J Am Coll Cardiol,2019,73(8):948-963.

[34] MØLLER S, WIESE S, BARLØSE M, et al. How non-alcoholic fatty liver disease and cirrhosis affect the heart[J]. Hepatol Int,2023,17(6):1333-1349.

[35] EL HADI H, DI VINCENZO A, VETTOR R, et al. Relationship between heart disease and liver disease: a two-way street[J]. Cells,2020,9(3):567.

[36] XIE W, GAN J, ZHOU X, et al. Myocardial infarction accelerates the progression of MASH by triggering immunoinflammatory response

and induction of periosti[J]. Cell Metab,2024,36(6):1269-1286.
[37] FORTEA J I, PUENTE Á, CUADRADO A, et al. Congestive Hepatopathy[J]. Int J Mol Sci,2020,21(24):9420.
[38] THEODORAKIS N, NIKOLAOU M. From cardiovascular-kidney-metabolic syndrome to cardiovascular-renal-hepatic-metabolic syndrome: proposing an expanded framework[J]. Biomolecules,2025,15(2):213.
[39] IVANCOVSKY WAJCMAN D, NICOLÀS A, PICCHIO C A, et al. Prioritising viral hepatitis elimination to prevent hepatocellular carcinoma: a public health approach for effective preventive hepatology[J]. JHEP Rep,2025,7(8):101436.
[40] XU R, LIU B, ZHOU X. Comparison of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter protein-2 inhibitors on treating metabolic dysfunction-associated steatotic liver disease or metabolic dysfunction-associated steatohepatitis: systematic review and network meta-analysis of randomised controlled trials[J]. Endocr Pract,2025,31(4):521-535.
[41] FERREIRA J P, JHUND P S, DUARTE K, et al. Use of the win ratio in cardiovascular trials[J]. JACC Heart Fail,2020,8(6):441-450.
[42] DUFOUR J F, ANSTEE Q M, BUGIANESI E, et al. Current therapies and new developments in NASH[J]. Gut,2022,71(10):2123-2134.
[43] ZANNAD F, SANYAL A J, BUTLER J, et al. Integrating liver endpoints in clinical trials of cardiovascular and kidney disease[J]. Nat Med,2024,30(9):2423-2431.
[44] ZANNAD F, SANYAL A J, BUTLER J, et al. MASLD and MASH at the crossroads of hepatology trials and cardiorenal metabolic trials[J]. J Intern Med,2024,296(1):24-38.
[45] ARMSTRONG P W, WESTERHOUT C M. Composite end points in clinical research: a time for reappraisal[J]. Circulation,2017,135(23):2299-2307.
[46] ARNETT D K, BLUMENTHAL R S, ALBERT M A, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines[J]. Circulation,2019,140(11):e596-e646.
[47] COREY K E, KLEBANOFF M J, TRAMONTANO A C, et al. Screening for nonalcoholic steatohepatitis in individuals with type 2 diabetes: a cost-effectiveness analysis[J]. Dig Dis Sci,2016,61(7):2108-2117.
[48] ESLAM M, FAN J G, YU M L, et al. The Asian Pacific association for the study of the liver clinical practice guidelines for the diagnosis and management of metabolic dysfunction-associated fatty liver disease[J]. Hepatol Int,2025,19(2):261-301.
[49] MIELE L, ZOCCO M A, PIZZOLANTE F, et al. Use of imaging techniques for non-invasive assessment in the diagnosis and staging of non-alcoholic fatty liver disease[J]. Metabolism,2020,112:154355.
[50] VILAR-GOMEZ E, CHALASANI N. Non-invasive assessment of non-alcoholic fatty liver disease: Clinical prediction rules and blood-based biomarkers[J]. J Hepatol,2018,68(2):305-315.
[51] BRIL F, MCPHAUL M J, CAULFIELD M P, et al. Performance of plasma biomarkers and diagnostic panels for nonalcoholic steatohepatitis and advanced fibrosis in patients with type 2 diabetes[J]. Diabetes Care,2020,43(2):290-297.
[52] ZHANG X, WONG G L, WONG V W. Application of transient elastography in nonalcoholic fatty liver disease[J]. Clin Mol Hepatol,2020,26(2):128-141.
[53] ADAMS L A, THIELE M, TSOCHATZIS E A. Detecting at-risk steatotic liver disease and liver fibrosis in the community[J/OL]. (2025-05-16)[2025-09-20]. https://journals.lww.com/hep/fulltext/9900/detecting_at_risk_steatotic_liver_disease_and.1285.aspx
[54] CONGLY S E, SHAHEEN A A, SWAIN M G. Modelling the cost effectiveness of non-alcoholic fatty liver disease risk stratification strategies in the community setting[J]. PLoS One,2021,16(5):e0251741.
[55] ASPHAUG L, THIELE M, KRAG A, et al. Cost-effectiveness of noninvasive screening for alcohol-related liver fibrosis[J]. Hepatology, 2020,71(6):2093-2104.
[56] FORLANO R, STANIC T, JAYAWARDANA S, et al. A prospective study on the prevalence of MASLD in people with type-2 diabetes in the community. Cost effectiveness of screening strategies[J]. Liver Int,2024,44(1):61-71.
[57] RINELLA M E, NEUSCHWANDER-TETRI B A, SIDDIQUI M S, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease[J]. Hepatology, 2023,77(5):1797-1835.
[58] CHEW N W S, MEHTA A, GOH R S J, et al. Cardiovascular-liver-metabolic health: recommendations in screening, diagnosis, and management of metabolic dysfunction-associated steatotic liver disease in cardiovascular disease via modified delphi approach[J]. Circulation,2025,151(1):98-119.
[59] STEFAN N, HÄRING H U, CUSI K. Non-alcoholic fatty liver disease: causes, diagnosis, cardiometabolic consequences, and treatment strategies[J]. Lancet Diabetes Endocrinol,2019,7(4):313-324.
[60] PETRONI M L, BRODOSI L, BUGIANESI E, et al. Management of non-alcoholic fatty liver disease[J]. BMJ,2021,372:m4747.
[61] ALA M, EFTEKHAR S P. Weight loss breaks the bond between nonalcoholic fatty liver disease and cardiovascular diseases: a clinical and epidemiological perspective[J]. Obes Rev,2023,24(6):e13563.
[62] Look AHEAD Research Group. Association of the magnitude of weight loss and changes in physical fitness with long-term cardiovascular disease outcomes in overweight or obese people with type 2 diabetes: a post-hoc analysis of the Look AHEAD randomised clinical trial[J]. Lancet Diabetes Endocrinol,2016,4(11):913-921.
[63] WIGGINS T, GUIDOZZI N, WELBOURN R, et al. Association of bariatric surgery with all-cause mortality and incidence of obesity-related disease at a population level: A systematic review and meta-analysis[J]. PLoS Med,2020,17(7):e1003206.
[64] DE LUCA M, ANGRISANI L, HIMPENS J, et al. Indications for surgery for obesity and weight-related diseases: position statements from the International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO)[J]. Obes Surg,2016,26(8):1659-1696.
[65] KINDEL T L, STRANDE J L. Bariatric surgery as a treatment for heart failure: review of the literature and potential mechanisms[J]. Surg Obes Relat Dis,2018,14(1):117-122.
[66] LIM C P, FISHER O M, FALKENBACK D, et al. Bariatric surgery provides a “bridge to transplant” for morbidly obese patients with advanced heart failure and may obviate the need for transplantation[J]. Obes Surg,2016,26(3):486-493.
[67] ORCI L A, GARIANI K, OLDANI G, et al. Exercise-based interventions for nonalcoholic fatty liver disease: a Meta-analysis and Meta-regression[J]. Clin Gastroenterol Hepatol,2016,14(10):1398-1411.
[68] WAHID A, MANEK N, NICHOLS M, et al. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and Meta-Analysis[J]. J Am Heart Assoc,2016,5(9):e002495.
[69] SATTELMAIR J, PERTMAN J, DING E L, et al. Dose response between physical activity and risk of coronary heart disease: a meta-analysis[J]. Circulation,2011,124(7):789-795.
[70] VILAR-GOMEZ E, MARTINEZ-PEREZ Y, CALZADILLA-BERTOT L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis[J]. Gastroenterology, 2015,149(2):367-378.e5.
[71] LARSON-MEYER D E, HEILBRONN L K, REDMAN L M, et al. Effect of calorie restriction with or without exercise on insulin sensitivity, beta-cell function, fat cell size, and ectopic lipid in overweight subjects[J]. Diabetes Care,2006,29(6):1337-1344.
[72] TSOMPANAKI E, THANAPIROM K, PAPATHEODORIDI M, et al. Systematic review and meta-analysis: the role of diet in the development of nonalcoholic fatty liver disease[J]. Clin Gastroenterol Hepatol,2023,21(6):1462-1474.
[73] PROPERZI C, O’SULLIVAN T A, SHERRIFF J L, et al. Ad Libitum Mediterranean and low-fat diets both significantly reduce hepatic steatosis: a randomized controlled trial[J]. Hepatology, 2018,68(5):1741-1754.
[74] KAWAGUCHI T, CHARLTON M, KAWAGUCHI A, et al. Effects of Mediterranean diet in patients with nonalcoholic fatty liver disease: a systematic review, meta-analysis, and meta-regression analysis of randomized controlled trials[J]. Semin Liver Dis,2021,41(3):225-234.
[75] DEL BO’ C, PERNA S, ALLEHDAN S, et al. Does the Mediterranean diet have any effect on lipid profile, central obesity and liver enzymes in non-alcoholic fatty liver disease (NAFLD) subjects? A

systematic review and meta-analysis of randomized control trials[J]. Nutrients,2023,15(10):2250.
[76] MA Y, YANG W, SIMON T G, et al. Dietary patterns and risk of hepatocellular carcinoma among U S men and women[J]. Hepatology,2019,70(2):577-586.
[77] CAPONE F, VETTOR R, SCHIATTARELLA G G. Cardiometabolic HPpEF: NASH of the heart[J]. Circulation,2023,147(6):451-453.
[78] DANIELS S, KARLSSON C, SCHRAUWEN P, et al. Glucagon-like peptide-1 receptor agonism and end-organ protection[J]. Trends Endocrinol Metab,2025,36(4):301-315.
[79] COSKUN T, URVA S, ROELL W C, et al. LY3437943, a novel triple glucagon, GIP, and GLP-1 receptor agonist for glycemic control and weight loss: From discovery to clinical proof of concept[J]. Cell Metab,2022,34(9):1234-1247.
[80] BOLAND M L, LAKER R C, MATHER K, et al. Resolution of NASH and hepatic fibrosis by the GLP-1R/GcgR dual-agonist Cotadutide via modulating mitochondrial function and lipogenesis[J]. Nat Metab,2020,2(5):413-431.
[81] NEWSOME P N, AMBERY P. Incretins (GLP-1 receptor agonists and dual/triple agonists) and the liver[J]. J Hepatol,2023,79(6):1557-1565.
[82] TOWNSEND L K, STEINBERG G R. AMPK and the endocrine control of metabolism[J]. Endocr Rev,2023,44(5):910-933.
[83] SOUZA M, AL-SHARIF L, ANTUNES V L J, et al. Comparison of pharmacological therapies in metabolic dysfunction-associated steatohepatitis for fibrosis regression and MASH resolution: Systematic review and network meta-analysis[EB/OL]. (2025-02-04)[2025-09-20]. https://journals.lww.com/hep/fulltext/9900/comparison_of_pharmacological_therapies_in.1156.aspx.
[84] SANYAL A J, NEWSOME P N, KLIERS I, et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis[J]. N Engl J Med,2025,392(21):2089-2099.
[85] LOOMBA R, HARTMAN M L, LAWITZ E J, et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis[J]. N Engl J Med,2024,391(4):299-310.
[86] MARSO S P, BAIN S C, CONSOLI A, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes[J]. N Engl J Med,2016,375(19):1834-1844.
[87] LINCOFF A M, BROWN-FRANDSEN K, COLHOUN H M, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes[J]. N Engl J Med,2023,389(24):2221-2232.
[88] KOSIBOROD M N, DEANFIELD J, PRATLEY R, et al. Semaglutide versus placebo in patients with heart failure and mildly reduced or preserved ejection fraction: a pooled analysis of the SELECT, FLOW, STEP-HPpEF, and STEP-HPpEF DM randomised trials[J]. Lancet,2024,404(10456):949-961.
[89] TACKE F, PUENGEL T, LOOMBA R, et al. An integrated view of anti-inflammatory and antifibrotic targets for the treatment of NASH[J]. J Hepatol,2023,79(2):552-566.
[90] CARLI F, DELLA PEPA G, SABATINI S, et al. Lipid metabolism in MASLD and MASH: from mechanism to the clinic[J]. JHEP Rep,2024,6(12):101185.
[91] DE CARVALHO L S F, NOGUEIRA A C C, BONILHA I, et al. Glucose-lowering and the risk of cardiovascular events with antidiabetic therapies: a systematic review and additive-effects network meta-analysis[J]. Front Cardiovasc Med,2022,9:876795.
[92] ZHOU X D, LIU W Y, TARGHER G, et al. Letter: drug interaction in resmetirom times[J]. Aliment Pharmacol Ther,2024,60(4):533-534.
[93] TRAN Q T, BUI T T, NGO L T, et al. Model-based meta-analysis of the relationship between pioglitazone and histological outcomes in metabolic dysfunction-associated steatohepatitis patients[EB/OL]. (2025-04-18)[2025-09-20]. https://ascpt.onlinelibrary.wiley.com/doi/10.1002/psp4.70034.
[94] American Diabetes Association Professional Practice Committee. Comprehensive medical evaluation and assessment of comorbidities: standards of care in diabetes-2025[J]. Diabetes Care,2025,48(1 Suppl 1):S59-S85.
[95] GAWRIEH S, NOUREDDIN M, LOO N, et al. Saroglitazar, a PPAR-α/γ agonist, for treatment of NAFLD: a randomized controlled double-blind phase 2 trial[J]. Hepatology,2021,74(4):1809-1824.
[96] SIDDIQUI M S, IDOWU M O, PARMAR D, et al. A phase 2 double blinded, randomized controlled trial of saroglitazar in patients with nonalcoholic steatohepatitis[J]. Clin Gastroenterol Hepatol,2021,19(12):2670-2672.
[97] SIDDIQUI M S, PARMAR D, SHEIKH F, et al. Saroglitazar, a dual PPAR α/γ agonist, improves atherogenic dyslipidemia in patients with non-cirrhotic nonalcoholic fatty liver disease: a pooled analysis[J]. Clin Gastroenterol Hepatol,2023,21(10):2597-2605.
[98] LOOMBA R, BEDOSSA P, GRIMMER K, et al. Denifanstat for the treatment of metabolic dysfunction-associated steatohepatitis: a multicentre, double-blind, randomised, placebo-controlled, phase 2b trial[J]. Lancet Gastroenterol Hepatol,2024,9(12):1090-1100.
[99] SANYAL A J, RATZIU V, LOOMBA R, et al. Results from a new efficacy and safety analysis of the REGENERATE trial of obeticholic acid for treatment of pre-cirrhotic fibrosis due to non-alcoholic steatohepatitis[J]. J Hepatol,2023,79(5):1110-1120.
[100] CALLE R A, AMIN N B, CARVAJAL-GONZALEZ S, et al. ACC inhibitor alone or co-administered with a DGAT2 inhibitor in patients with non-alcoholic fatty liver disease: two parallel, placebo-controlled, randomized phase 2a trials[J]. Nat Med,2021,27(10):1836-1848.
[101] CHOU R, DANA T, BLAZINA I, et al. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force[J]. JAMA,2016,316(19):2008-2024.
[102] ZHOU X D, MUTHIAH M D, ZHENG M. Statins in MASLD: Challenges and Future[EB/OL]. (2025-02-26)[2025-09-20]. https://www.sciencedirect.com/science/article/pii/S2589555925000497.
[103] ZHOU X D, KIM S U, YIP T C, et al. Long-term liver-related outcomes and liver stiffness progression of statin usage in steatotic liver disease[J]. Gut,2024,73(11):1883-1892.
[104] CHOI J, NGUYEN V H, PRZYBYSZEWSKI E, et al. Statin use and risk of hepatocellular carcinoma and liver fibrosis in chronic liver disease[J]. JAMA Intern Med,2025,185(5):522-530.
[105] LATVA-RASKU A, HONKA M J, KULLBERG J, et al. The SGLT2 inhibitor dapagliflozin reduces liver fat but does not affect tissue insulin sensitivity: a randomized, double-blind, placebo-controlled study with 8-week treatment in type 2 diabetes patients[J]. Diabetes Care,2019,42(5):931-937.
[106] SIAFARIKAS C, KAPELIOS C J, PAPATHEODORIDI M, et al. Sodium-glucose linked transporter 2 inhibitors in liver cirrhosis: Beyond their antidiabetic use[J]. Liver Int,2024,44(4):884-893.
[107] LIN J, HUANG Y, XU B, et al. Effect of dapagliflozin on metabolic dysfunction-associated steatohepatitis: multicentre, double blind, randomised, placebo controlled trial[J]. BMJ,2025,389:e083735.
[108] SIMON T G, WILECHANSKY R M, STOYANOVA S, et al. Aspirin for metabolic dysfunction-associated steatotic liver disease without cirrhosis: a randomized clinical trial[J]. JAMA,2024,331(11):920-929.
[109] GOH G B, PAGADALA M R, DASARATHY J, et al. Renin-angiotensin system and fibrosis in non-alcoholic fatty liver disease[J]. Liver Int,2015,35(3):979-985.
[110] ZHANG X, WONG G L, YIP T C, et al. Angiotensin-converting enzyme inhibitors prevent liver-related events in nonalcoholic fatty liver disease[J]. Hepatology,2022,76(2):469-482.

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