Journal of Clinical Personalized Medicine 临床个性化医学, 2025, 4(3), 730-738
Published Online June 2025 in Hans. https://www.hanspub.org/journal/jcpm
https://doi.org/10.12677/jcpm.2025.43402

GLP-1受体激动剂在代谢功能障碍相关脂肪性肝病治疗中的研究进展

陈舒婷[1]，刘　瑛[2]，张　弛[2*]

[1]湖南师范大学附属第一医院(湖南省人民医院)内分泌科，湖南　长沙
[2]湖南省人民医院(湖南师范大学附属第一医院)内分泌科，湖南　长沙

收稿日期：2025年5月26日；录用日期：2025年6月18日；发布日期：2025年6月27日

摘　要

代谢功能障碍相关脂肪性肝病(MASLD)是一种与多种代谢异常密切相关的慢性肝脏疾病，其核心病理特征为脂肪在肝细胞内异常堆积，且排除其他已知致病因素，如酒精性肝病、病毒性肝炎及自身免疫性疾病等。MASLD与代谢综合征和2型糖尿病之间相互影响，共同促进动脉粥样硬化性心脏病、慢性肾脏病及肝细胞癌等恶性肿瘤等多种并发症的发生。这种复杂的代谢网络使得MASLD成为日益严峻的公共卫生问题。2024年，瑞美替罗成为首个获美国食品药品监督管理局批准用于治疗MASH的药物，然而针对MASLD的早期阶段仍缺乏获批药物。在此背景下，胰高血糖素样肽-1 (GLP-1)受体激动剂因其独特的多靶点调控作用，在MASLD治疗中展现出显著的临床应用潜力。本研究旨在系统分析GLP-1受体激动剂在MASLD治疗中的作用机制，并结合循证医学证据评估其疗效与安全性，为临床实践提供理论依据。

关键词

代谢功能障碍相关脂肪性肝病，胰高血糖素样肽-1受体激动剂，肝纤维化，肝脂肪变性，胰岛素抵抗

Research Progress of GLP-1 Receptor Agonists in the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease

Shuting Chen[1], Ying Liu[2], Chi Zhang[2*]

[1]Department of Endocrinology, The First Affiliated Hospital of Hunan Normal University (Hunan Provincial People's Hospital), Changsha Hunan
[2]Department of Endocrinology, Hunan Provincial People's Hospital (The First Affiliated Hospital of Hunan

[*]通讯作者。

文章引用: 陈舒婷, 刘瑛, 张弛. GLP-1 受体激动剂在代谢功能障碍相关脂肪性肝病治疗中的研究进展[J]. 临床个性化医学, 2025, 4(3): 730-738. DOI: 10.12677/jcpm.2025.43402

Normal University), Changsha Hunan

Received: May 26th, 2025; accepted: Jun. 18th, 2025; published: Jun. 27th, 2025

Abstract

Metabolic dysfunction-associated fatty liver disease (MASLD) is a chronic liver disease closely related to a variety of metabolic abnormalities, and its core pathological feature is abnormal accumulation of fat in hepatocytes, and other known pathogenic factors, such as alcoholic liver disease, viral hepatitis and autoimmune diseases, are excluded. MASLD interacts with metabolic syndrome and type 2 diabetes mellitus, and jointly promotes the occurrence of various complications such as atherosclerotic heart disease, chronic kidney disease, and hepatocellular carcinoma. This complex metabolic network makes MASLD a growing public health problem. In 2024, remettirol became the first drug approved by the U.S. Food and Drug Administration for the treatment of MASH, although there is still a lack of approved drugs for MASLD in the early stages. In this context, glucagon-like peptide-1 (GLP-1) receptor agonists have shown significant clinical application potential in the treatment of MASLD due to their unique multi-target regulatory effects. The purpose of this study was to systematically analyze the mechanism of action of GLP-1 receptor agonists in the treatment of MASLD, and to evaluate their efficacy and safety based on evidence-based medical evidence, so as to provide a theoretical basis for clinical practice.

Keywords

Metabolic Dysfunction-Associated Fatty Liver Disease, Glucagon-Like Peptide-1 Receptor Agonists, Liver Fibrosis, Hepatic Steatosis, Insulin Resistance

1. 代谢功能障碍相关脂肪性肝病的概况和流行病学现状

代谢功能障碍相关脂肪性肝病(Metabolic Dysfunction-Associated Steatotic Liver Disease, MASLD)是一种在遗传易感个体中发生的慢性肝脏疾病，其核心驱动因素为胰岛素抵抗和营养过剩[1]。如今，MASLD已成为全球最常见的慢性肝病，影响着约 30%的成年人口，其中，拉丁美洲和西欧的患病率较高，分别达到 44%和 25.1% [2]。在中国，MASLD 已取代病毒性肝炎成为第一大慢性肝病，这与肥胖率上升、代谢综合征增加以及病毒性肝炎防控成效显著密切相关[3]。MASLD 的疾病谱呈现出一个连续的病理过程，从单纯性脂肪变性、代谢相关脂肪性肝炎(Metabolic Dysfunction-Associated Steatohepatitis, MASH)，逐步发展到进行性肝纤维化、肝硬化，甚至肝细胞癌(Hepatocellular Carcinoma, HCC) [4]。约 20%的 MASLD 患者会发展为 MASH，其中 10%~20%可能进展至肝硬化。在全球范围内，MASLD 相关的肝硬化和 HCC 发病率呈逐年上升趋势。截至 2023 年，MASLD 相关的终末期肝病已成为肝移植的第二大适应症，仅次于酒精性肝病[5]。心血管疾病是 MASLD 患者的主要死因，其风险较普通人群增加 38%~40% [6]。MASLD 的前身是非酒精性脂肪性肝病(NAFLD)。2020 年，国际专家小组提议将 NAFLD 更名为 MAFLD，旨在强调代谢功能障碍在该疾病中的核心地位。2023 年 6 月美国肝病研究学会年会上提出将 MAFLD 更名为 MASLD，规范了诊断标准并突出疾病的异质性[7]。通过回顾性分析流行病学调查数据可知，超过 95%的

NAFLD 患者符合 MASLD 的诊断标准，所以以往针对 NAFLD 的研究数据可类推应用于 MASLD 人群[8]。尽管 MASLD 在全球范围内造成了巨大的健康威胁，但由于单纯肝脏脂肪变性患者出现肝脏不良结局的风险较低，人群普遍对其重视程度不够，且目前缺乏特异性筛查手段，导致超半数 MASLD 病例仍未被确诊[9]。MASLD 造成的社会经济负担也很突出。以美国为例，MASLD 的直接医疗成本高达 1030 亿美元，超过德国、法国和意大利三国总和[10]。预计在未来十年，美国因 MASLD 产生的总负担将达 1.005 万亿美元，欧洲则为 3340 亿欧元。MASLD 不仅损害肝脏健康，还与代谢综合征和 T2DM 相互影响，显著提升了动脉粥样硬化性心脏疾病、慢性肾脏病及肝细胞癌等恶性肿瘤的发生风险，导致显著的全因死亡率[11]，对患者的生命质量和预期寿命构成严重威胁。

2. 代谢功能障碍相关脂肪性肝病的发病机制

首先需先探讨 MASLD 的发病机制，MASLD 的病理发生涉及多系统相互作用，其核心机制主要包括脂质代谢失衡、氧化应激、炎症反应、胰岛素抵抗等多个关键环节，各通路间形成恶性循环，共同驱动疾病进展。

2.1. 脂质代谢失衡

肝脏脂质代谢稳态失衡是 MASLD 发病的始动因素，主要表现为脂肪生成增加与脂质排出障碍。在胰岛素抵抗和高胰岛素血症的病理条件下，固醇调节元件结合蛋白 1c (SREBP-1c)被异常激活，进而上调乙酰辅酶 A 羧化酶(ACC)和脂肪酸合酶(FAS)的表达水平，促进脂肪酸的从头合成，最终导致新生脂肪生成显著增强[12]。此外，载脂蛋白 B(ApoB)合成减少与微粒体甘油三酯转移蛋白(MTP)活性受到抑制，共同导致肝脏无法有效将甘油三酯(TG)包装成极低密度脂蛋白(VLDL)并分泌进入血液循环中，从而使脂质在肝细胞内大量蓄积[13] [14]。此外，MASLD 患者的高密度脂蛋白(HDL)水平降低，导致胆固醇逆向转运能力下降[15]，进一步加剧脂毒性微环境的形成，为后续炎症反应和纤维化进程提供了病理基础。脂质代谢异常导致脂肪在肝脏中的堆积，通过激活多种信号通路，引发一系列代谢异常和炎症反应。这种代谢–炎症的级联反应不仅加重了肝脏损伤，还通过系统性炎症影响全身代谢稳态。

2.2. 氧化应激

氧化应激是 MASLD 病理过程中重要驱动因素之一，其本质是活性氧(ROS)的过度积累与抗氧化防御系统失衡。脂肪在肝脏中的堆积会引发线粒体功能障碍，破坏 ROS 生成与清除之间的动态平衡[16]。过量的 ROS 通过脂质过氧化反应破坏细胞膜结构，损伤蛋白质和 DNA，并激活炎症级联反应及纤维化进程[17]。研究发现，这一过程与内质网应激密切相关，可能通过 XBP1s 信号通路的异常进一步推动病理进展[18]。

2.3. 炎症反应

炎症反应不仅直接导致肝细胞损伤，还通过激活纤维化和胰岛素抵抗等途径促进疾病进展。肝细胞在脂肪堆积和氧化应激的双重作用下发生损伤乃至坏死，这一过程通过释放损伤相关分子模式(DAMPs)启动炎症级联反应。DAMPs 作为内源性危险信号，能够激活核因子 κB (NF-κB)、c-Jun 氨基末端激酶(JNK)和 NLRP3 炎症小体等关键信号通路，上述信号通路的激活导致肿瘤坏死因子 α (TNF-α)、白细胞介素 6 (IL-6)等促炎因子分泌增多。这些细胞因子的释放触发免疫细胞的募集过程，包括巨噬细胞、中性粒细胞和 T 细胞等免疫细胞在肝脏中的浸润。这些免疫细胞的活化及其分泌的细胞因子共同构成了复杂的炎症网络，推动疾病向纤维化阶段进展[19]-[21]。

2.4. 胰岛素抵抗

胰岛素抵抗的本质是机体对胰岛素生物效应的敏感性下降，导致胰岛素信号传导障碍，进而引起糖脂代谢紊乱。在 MASLD 患者中，胰岛素抵抗主要累及肝脏、脂肪组织和骨骼肌三大代谢关键器官，形成复杂的代谢网络失衡。肝脏的胰岛素信号通路受损导致糖异生增加，进而引发肝糖输出增加和糖原合成减少，导致空腹高血糖[22] [23]。同时脂肪组织对胰岛素的抗脂解作用减弱，导致激素敏感性脂肪酶(HSL)的活性升高，这种改变促使大量游离脂肪酸释放进入血液循环[24]，通过门静脉系统转运至肝脏。在肝细胞内，这些脂肪酸被重新酯化为甘油三酯，进一步加剧肝脂肪变性的病理进程。此外，骨骼肌作为胰岛素敏感组织，其葡萄糖转运蛋白 4 (GLUT4)的转位减少，导致葡萄糖摄取和利用能力下降[25]。同时，骨骼肌中脂肪酸氧化能力降低，造成脂质在肌肉细胞内异常蓄积。这种双重代谢障碍不仅加重了全身性胰岛素抵抗，还通过脂毒性作用进一步损害骨骼肌功能。

除上述机制外，肠道菌群失调、遗传变异、线粒体功能障碍等因素也可能参与 MASLD 的发病过程。这些因素与脂质代谢失衡、氧化应激、炎症反应、胰岛素抵抗等机制相互作用，共同构成了 MASLD 复杂的病理网络。这种多因素交互作用的特点凸显了 MASLD 发病机制的高度复杂性及其治疗难度。

3. GLP-1 受体激动剂治疗 MASLD 的潜在作用机制

作为一类新型肠促胰岛素类药物，胰高血糖素样肽-1 (GLP-1)受体激动剂最初获得批准用于 2 型糖尿病(T2DM)和肥胖症的治疗。近年来，随着研究的深入，其在 MASLD 及 MASH 治疗中展现出多靶点治疗潜力，涵盖了改善肝脏脂肪变性、调控氧化应激、抑制炎症反应、调节胰岛素抵抗及延缓肝脏纤维化等多个关键环节。

3.1. 改善肝脏脂肪变性

脂毒性损伤的缓解涉及对 SREBP-1c 信号轴的深度调控。临床前研究发现，GLP-1 受体激动剂通过抑制固醇调节元件结合蛋白 1c (SREBP-1c)及其下游靶基因脂肪酸合成酶 FASN、乙酰辅酶 A 羧化酶 ACC 的表达，使新生脂肪生成减少[26]。研究显示，司美格鲁肽表现出独立于体重减轻的肝脏脂质清除效应，这与其对肝细胞线粒体功能的直接作用密切相关[16]。PPAR-α 通路的上调增强了脂肪酸 β 氧化能力，使肝内甘油三酯分解速率提升[27]。临床研究数据显示，司美格鲁肽治疗 24 周可使 MASLD 患者肝脏脂肪含量(LFC)绝对降幅达 18.3%，HOMA-IR 指数改善 32.4% [28]。同时，有长期随访数据显示，艾塞那肽治疗 3 年可使 41%MASLD 患者的 ALT 水平完全正常化，肝脏脂肪逆转率达到 66.7%，显著优于强化胰岛素组($p < 0.01$) [29]。一项 II 期临床试验结果证实，利拉鲁肽治疗可显著改善 MASLD 患者脂肪变性(利拉鲁肽组 83% vs. 安慰剂组 45%)，同时有效抑制肝纤维化进展(利拉鲁肽组 9% vs. 安慰剂组 36%)，患者体重平均减轻 5.5 kg (安慰剂组 0.6 kg) [30]。Meta 分析进一步证实，对于 MASLD 合并 T2DM 或肥胖的进展期患者，相较于 PPAR 激动剂侧重体重调控，GLP-1 受体激动剂在改善脂肪变性方面具有最优效应量(SMD = −0.43, $p < 0.01$) [31]。

3.2. 调控氧化应激

GLP-1 受体激动剂通过激活抗氧化防御系统、改善线粒体功能、调控内质网氧化应激等多重机制，形成了协同作用网络，有效调控氧化应激。GLP-1 受体激动剂激活 Nrf2-ARE 通路，使超氧化物歧化酶(SOD)和谷胱甘肽过氧化物酶(GPx)的活性增加，激活抗氧化防御系统，从而降低脂质过氧化产物水平[32]。动物模型中，exendin-4 处理显著降低高脂模型小鼠肝脂含量及脂质过氧化产物水平[33]。GLP-1 受体激动剂通过抑制 c-Jun 氨基末端激酶(JNK)信号通路，改善肝细胞线粒体功能，阻断氧化应激与炎症反

应的恶性循环[34]。研究表明，司美格鲁肽具有独立于体重减轻的独特作用，能够显著减少内质网氧化应激[16]。

3.3. 抑制炎症反应

GLP-1 受体激动剂通过多种机制协同作用，有效抑制炎症反应，从而改善 MASLD 患者的炎症微环境。GLP-1 受体激动剂通过阻断 NF-κB 核转位，可以使 TNF-α、IL-1β等促炎因子的表达水平降低 50%~60%，临床实验显示 CRP 水平平均下降 15%~20% [35]。另外，丙氨酸氨基转移酶(ALT)作为肝细胞损伤的重要标志物，其水平升高直接反映了 MASLD 患者存在肝脏炎症。事实上，患有 MASLD 和 ALT 升高的患者进展为 MASH 和肝硬化的风险增加。在一项关于司美格鲁肽对体重和心血管影响的临床试验分析中，该药物被证明可显著降低 T2DM 和/或肥胖患者的 ALT 水平[36]。

3.4. 调节胰岛素抵抗

GLP-1 受体激动剂通过激活多条信号通路，形成了改善胰岛素抵抗的协同效应网络。GLP-1 受体在人肝细胞膜表面存在明确表达，其激活可触发 cAMP-PKA 信号级联反应，同时增强 AMP 活化蛋白激酶(AMPK)依赖途径和 PI3K/Akt 通路活性[37]。研究显示，GLP-1 受体激活可激活腺苷酸环化酶(Adenylyl cyclase)，增加细胞内 cAMP 水平，进而激活蛋白激酶 A(PKA)，促进电压依赖性 Ca^{2+}通道开放，增加胞内 Ca^{2+}浓度，增强葡萄糖依赖性胰岛素分泌，改善肝细胞对胰岛素的敏感性[38]。GLP-1 还可以通过激活 AMPK(腺苷酸活化蛋白激酶)，抑制乙酰辅酶 A 羧化酶(ACC)，减少脂肪酸合成，同时促进脂肪酸氧化，减少脂质沉积，从而改善胰岛素敏感性[39]。GLP-1 受体激动剂通过激活 PI3K/AKT 通路，使 AKT 磷酸化，直接抑制糖异生关键酶磷酸烯醇式丙酮酸羧激酶(PEPCK)和葡萄糖-6-磷酸酶(G6Pase)的表达，使肝糖输出量降低 40%，上调胰岛素受体底物 1 (IRS-1)磷酸化水平，从而改善肝脏对胰岛素的敏感性[40]。同时 GLP-1 受体激动剂还可抑制 HSL，使循环游离脂肪酸水平下降 25%~30%，间接缓解脂毒性对胰岛素信号的干扰[41]。

3.5. 延缓肝脏纤维化

多项随机对照试验证实 GLP-1 受体激动剂对肝脏纤维化的改善作用。有实验发现，GLP-1 受体激动剂可通过抑制 TGF-β/Smad 信号通路，显著降低 I 型胶原 α1 链(COL1A1)和 α-平滑肌肌动蛋白(α-SMA)的表达水平[42]。在具有里程碑意义的 LEAN 研究中，利拉鲁肽 1.8 mg/d 治疗 48 周使 39%的 MASH 患者实现脂肪性肝炎消退，纤维化进展率从安慰剂组的 36%降至 9% ($p = 0.04$)，这种效应在调整体重变化后仍保持统计学意义[43]。然而虽然 GLP-1 受体激动剂能减缓肝纤维化进展，但未被证实可逆转纤维化。临床指南明确指出[44]，现有 GLP-1 受体激动剂仅能缓解 MASH 并减缓纤维化进展，但无法逆转纤维化。研究发现，GLP-1 受体激动剂对纤维化逆转效果不明显，但新型双重受体激动剂(如替尔泊肽)或联合疗法(如 SGLT2 抑制剂 + GLP-1RA)在临床试验中显示出更优潜力[22] [45]。尽管逆转已有纤维化需更长期治疗，但现有数据表明 GLP-1 受体激动剂可有效阻止疾病向肝硬化进展。

GLP-1 受体激动剂通过多靶点作用机制，在 MASLD 及其进展型 MASH 的治疗中展现出显著的临床效果。其在改善肝脏脂肪变性、抑制炎症反应、调控氧化应激、调节胰岛素抵抗及延缓纤维化方面的综合疗效为其在代谢性肝病治疗中的广泛应用奠定了坚实基础。未来研究可进一步探索其在逆转纤维化和预防肝硬化方面的潜力。

4. GLP-1 受体激动剂在 MASLD 治疗中的安全性

MASLD 治疗的安全性评估是决定 GLP-1 受体激动剂临床转化价值的重要考量因素。尽管 GLP-1 受

体激动剂通过多重代谢调控途径为 MASLD 患者带来显著的治疗获益，但其潜在的不良反应和生物学效应仍需深入关注。现有临床证据表明，该类药物的安全性特征呈现出时间动态性和剂量依赖性的特点。从不良反应的角度来看，约 15%~30%的患者在初始治疗阶段可能出现恶心、呕吐或腹泻等消化道症状[46]，但绝大多数患者在持续用药 3~6 个月后可产生适应性耐受[29]。值得注意的是，高剂量组的不良反应发生风险较低剂量组更高[47]，这一剂量相关性特征值得临床中特别关注。尽管动物实验曾提示 GLP-1 类似物可能与甲状腺髓样癌风险增加相关[48]，但真实世界研究结果显示，治疗组甲状腺肿瘤发生率与普通人群无显著差异[49]。此外，在胰腺安全性方面，大规模队列研究显示 GLP-1 受体激动剂治疗者的急性胰腺炎年发生率为 0.11% [50]，表明其风险较低。在代谢特异性风险方面，近期一项由 8 项针对 T2DM 和 MASLD 的随机对照试验组成的荟萃分析指出，GLP-1 受体激动剂相关的主要不良事件包括轻度至中度的胃肠道不适和无意义低血糖，这些症状通常在几周内自行消退[51]。尽管 GLP-1RAs 本身并不直接刺激胰岛素分泌，但与其他降糖药物联用时，严重低血糖(血糖 < 3.0 mmol/L)的发生率上升，一项 Meta 分析指出，GLP-1 受体激动剂单用时风险较低，但与磺脲类联用时风险显著增加，与胰岛素联用风险更高[52]，提示临床中需根据患者具体情况调整用药剂量。在心血管系统安全性方面，GLP-1 受体激动剂表现出双重作用：一方面通过改善肝脏炎症状态降低患者心力衰竭住院风险[53]，另一方面可能引发心率增快[54]，因此对于基线 QT 间期延长的患者需加强监测。欧盟和美国 FDA 均要求药物说明书中明确将甲状腺髓样癌(MTC)个人或家族史、多发性内分泌肿瘤综合征 2 型(MEN2)列为 GLP-1 受体激动剂使用的禁忌症[55]。老年患者使用 GLP-1 受体激动剂可能导致过度体重下降、营养不良、低血压、脱水等风险。严重肾功能不全患者因缺乏排泄途径研究不推荐使用 GLP-1 受体激动剂[56]。GLP-1 受体激动剂还有可能导致其他罕见不良反应，2024 年一项回顾性研究(N = 2375)显示，GLP-1 受体激动剂相关肾损伤发生率为 58.65%，但仅 0.3%为严重事件[57]。约 10%患者出现局部红斑或硬结，与药物免疫原性相关。抗体阳性患者中过敏反应发生率可达 1.2%，包括荨麻疹和血管性水肿[58]。长期用药安全性数据表明，持续治疗 5 年以上的 MASLD 患者肝脏相关终点事件显著减少，肝硬化进展风险降低[59]，凸显了持续干预的重要性。综上所述，GLP-1 受体激动剂在 MASLD 治疗中的安全性表现总体可控，但需根据患者的具体情况制定个体化治疗方案，并密切监测潜在风险。

5. 小结

在全球范围内，肥胖与代谢紊乱问题逐年增长，MASLD 已成为最常见的慢性肝病。MASLD 的有效治疗与管理依赖多学科的协同合作，其治疗主要围绕多个目标展开：一是减轻体重与缩小腰围；二是改善胰岛素抵抗；三是防治代谢综合征和 T2DM；四是缓解 MASH，五是逆转肝脏纤维化。对于所有 MASLD 患者，开展健康教育并促进生活方式的改善是治疗的基石。在合并代谢性心血管危险因素或肝功能损伤的情况下，需要结合药物干预以达到更好的治疗效果。GLP-1 受体激动剂作为具备多靶点治疗特性的药物，在 MASLD 的治疗领域中呈现出显著的临床应用潜力。研究证实，GLP-1 受体激动剂具有改善肝脏脂肪变性、调控氧化应激反应、抑制炎症进程、调节胰岛素抵抗以及延缓肝脏纤维化等多种作用机制，为 MASLD 患者提供了全新的治疗选择。不过，现阶段关于 GLP-1 受体激动剂的临床研究尚不够全面。为了验证其安全性和有效性，需要开展更大规模、多中心的随机对照试验。同时，在长期用药过程中，还需关注可能出现的耐药性以及副作用等问题，以此明确 GLP-1 受体激动剂在 MASLD 全程管理中所具备的价值。随着多靶点药物研发工作的持续推进以及精准医学技术的不断进步，GLP-1 受体激动剂有望在 MASLD 的治疗中发挥更重要的作用。

项目来源

湖南省卫生健康委卫生科研重点指导课题(编号：202203062617)。

参考文献

[1] Bai, J., Zhu, L., Mi, W., Gao, Z., Ouyang, M., Sheng, W., *et al*. (2023) Multiscale Integrative Analyses Unveil Immune-Related Diagnostic Signature for the Progression of MASLD. *Hepatology Communications*, **7**, e0298. https://doi.org/10.1097/hc9.0000000000000298

[2] Yagüe-Caballero, C., Casas-Deza, D., Pascual-Oliver, A., Espina-Cadena, S., Arbones-Mainar, J.M. and Bernal-Monterde, V. (2024) MASLD-Related Hepatocarcinoma: Special Features and Challenges. *Journal of Clinical Medicine*, **13**, Article 4657. https://doi.org/10.3390/jcm13164657

[3] Dai, J., Liu, Y. and Zhang, Z. (2024) Changes in the Etiology of Liver Cirrhosis and the Corresponding Management Strategies. *World Journal of Hepatology*, **16**, 146-151. https://doi.org/10.4254/wjh.v16.i2.146

[4] European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) (2024) EASL-EASD-EASO Clinical Practice Guidelines on the Management of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). *Obesity Facts*, **17**, 374-444. https://doi.org/10.1159/000539371

[5] Kimura, Y., Tapia Sosa, R., Soto-Trujillo, D., Kimura Sandoval, Y. and Casian, C. (2020) Liver Transplant Complications Radiologist Can't Miss. *Cureus*, **12**, e8465. https://doi.org/10.7759/cureus.8465

[6] Mellemkjær, A., Kjær, M.B., Haldrup, D., Grønbæk, H. and Thomsen, K.L. (2024) Management of Cardiovascular Risk in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease. *European Journal of Internal Medicine*, **122**, 28-34. https://doi.org/10.1016/j.ejim.2023.11.012

[7] Targher, G., Byrne, C.D. and Tilg, H. (2024) MASLD: A Systemic Metabolic Disorder with Cardiovascular and Malignant Complications. *Gut*, **73**, 691-702. https://doi.org/10.1136/gutjnl-2023-330595

[8] Hagström, H., Vessby, J., Ekstedt, M. and Shang, Y. (2024) 99% of Patients with NAFLD Meet MASLD Criteria and Natural History Is Therefore Identical. *Journal of Hepatology*, **80**, e76-e77. https://doi.org/10.1016/j.jhep.2023.08.026

[9] Ossima, A.N., Brzustowski, A., Paradis, V., Van Beers, B., Postic, C., Laouénan, C., *et al*. (2024) Factors Associated with High Costs of Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease: An Observational Study Using the French Constances Cohort. *Clinical Diabetes and Endocrinology*, **10**, Article No. 9. https://doi.org/10.1186/s40842-023-00163-4

[10] Ang, S.M., Lim, S.L., Dan, Y.Y., Chan, Y.H., Yap, Q.V. and Chen, J. (2024) Clinical Service Incorporating Mobile Technology on Weight Loss in Patients with Metabolic Dysfunction-Associated Steatotic Liver Disease: A Translation from Research Trial. *Endocrinology, Diabetes & Metabolism*, **7**, e00485. https://doi.org/10.1002/edm2.485

[11] de Avila, L., Henry, L., Paik, J.M., Ijaz, N., Weinstein, A.A. and Younossi, Z.M. (2023) Nonalcoholic Fatty Liver Disease Is Independently Associated with Higher All-Cause and Cause-Specific Mortality. *Clinical Gastroenterology and Hepatology*, **21**, 2588-2596.e3. https://doi.org/10.1016/j.cgh.2023.01.006

[12] Hu, Y., Zai, H., Jiang, W., Ou, Z., Yao, Y. and Zhu, Q. (2021) The Mutual Inhibition of FoxO1 and SREBP-1c Regulated the Progression of Hepatoblastoma by Regulating Fatty Acid Metabolism. *Mediators of Inflammation*, **2021**, Article 5754592. https://doi.org/10.1155/2021/5754592

[13] Shreya, S., Grosset, C.F. and Jain, B.P. (2023) Unfolded Protein Response Signaling in Liver Disorders: A 2023 Updated Review. *International Journal of Molecular Sciences*, **24**, Article 14066. https://doi.org/10.3390/ijms241814066

[14] Khan, M.S., Lee, C. and Kim, S.G. (2022) Non-Alcoholic Fatty Liver Disease and Liver Secretome. *Archives of Pharmacal Research*, **45**, 938-963. https://doi.org/10.1007/s12272-022-01419-w

[15] Liao, M., Zhang, R., Wang, Y., Mao, Z., Wu, J., Guo, H., *et al*. (2022) Corilagin Prevents Non-Alcoholic Fatty Liver Disease via Improving Lipid Metabolism and Glucose Homeostasis in High Fat Diet-Fed Mice. *Frontiers in Nutrition*, **9**, Article 983450. https://doi.org/10.3389/fnut.2022.983450

[16] Shin, S., Kim, J., Lee, J.Y., Kim, J. and Oh, C. (2023) Mitochondrial Quality Control: Its Role in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). *Journal of Obesity & Metabolic Syndrome*, **32**, 289-302. https://doi.org/10.7570/jomes23054

[17] Koyama, H., Kamogashira, T. and Yamasoba, T. (2024) Heavy Metal Exposure: Molecular Pathways, Clinical Implications, and Protective Strategies. *Antioxidants*, **13**, Article 76. https://doi.org/10.3390/antiox13010076

[18] Liu, S., Ding, H., Li, Y. and Zhang, X. (2022) Molecular Mechanism Underlying Role of the XBP1s in Cardiovascular Diseases. *Journal of Cardiovascular Development and Disease*, **9**, Article 459. https://doi.org/10.3390/jcdd9120459

[19] Teuwen, J.T.J., van der Vorst, E.P.C. and Maas, S.L. (2024) Navigating the Maze of Kinases: CaMK-Like Family Protein Kinases and Their Role in Atherosclerosis. *International Journal of Molecular Sciences*, **25**, Article 6213. https://doi.org/10.3390/ijms25116213

[20] Yang, J., Zhong, C. and Yu, J. (2023) Natural Monoterpenes as Potential Therapeutic Agents against Atherosclerosis.

International Journal of Molecular Sciences, **24**, Article 2429. https://doi.org/10.3390/ijms24032429

[21] Ni, L., Yang, L. and Lin, Y. (2024) Recent Progress of Endoplasmic Reticulum Stress in the Mechanism of Atherosclerosis. *Frontiers in Cardiovascular Medicine*, **11**, Article 1413441. https://doi.org/10.3389/fcvm.2024.1413441

[22] Yanai, H., Adachi, H., Hakoshima, M., Iida, S. and Katsuyama, H. (2023) Metabolic-Dysfunction-Associated Steatotic Liver Disease—Its Pathophysiology, Association with Atherosclerosis and Cardiovascular Disease, and Treatments. *International Journal of Molecular Sciences*, **24**, Article 15473. https://doi.org/10.3390/ijms242015473

[23] Qiu, F., Wang, J., Liu, H. and Zhang, Y. (2019) Mulberry Bark Alleviates Effect of STZ Inducing Diabetic Mice through Negatively Regulating FoxO1. *Evidence-Based Complementary and Alternative Medicine*, **2019**, Article 2182865. https://doi.org/10.1155/2019/2182865

[24] Yin, C., Liu, W.H., Liu, Y., Wang, L. and Xiao, Y. (2019) PID1 Alters the Antilipolytic Action of Insulin and Increases Lipolysis via Inhibition of AKT/PKA Pathway Activation. *PLOS ONE*, **14**, e0214606. https://doi.org/10.1371/journal.pone.0214606

[25] Kim, M.J., Park, C.H., Kim, D.H., Park, M.H., Park, K.C., Hyun, M.K., *et al*. (2018) Hepatoprotective Effects of MHY3200 on High-Fat, Diet-Induced, Non-Alcoholic Fatty Liver Disease in Rats. *Molecules*, **23**, Article 2057. https://doi.org/10.3390/molecules23082057

[26] Parlevliet, E.T., Wang, Y., Geerling, J.J., Schröder-Van der Elst, J.P., Picha, K., O'Neil, K., *et al*. (2012) GLP-1 Receptor Activation Inhibits VLDL Production and Reverses Hepatic Steatosis by Decreasing Hepatic Lipogenesis in High-Fat-Fed APOE*3-Leiden Mice. *PLOS ONE*, **7**, e49152. https://doi.org/10.1371/journal.pone.0049152

[27] Winarto, J., Song, D. and Pan, C. (2023) The Role of Fucoxanthin in Non-Alcoholic Fatty Liver Disease. *International Journal of Molecular Sciences*, **24**, Article 8203. https://doi.org/10.3390/ijms24098203

[28] Drożdż, K., Nabrdalik, K., Hajzler, W., Kwiendacz, H., Gumprecht, J. and Lip, G.Y.H. (2021) Metabolic-Associated Fatty Liver Disease (MAFLD), Diabetes, and Cardiovascular Disease: Associations with Fructose Metabolism and Gut Microbiota. *Nutrients*, **14**, Article 103. https://doi.org/10.3390/nu14010103

[29] Chrysavgis, L.G., Kazanas, S., Bafa, K., Rozani, S., Koloutsou, M. and Cholongitas, E. (2024) Glucagon-Like Peptide 1, Glucose-Dependent Insulinotropic Polypeptide, and Glucagon Receptor Agonists in Metabolic Dysfunction-Associated Steatotic Liver Disease: Novel Medication in New Liver Disease Nomenclature. *International Journal of Molecular Sciences*, **25**, Article 3832. https://doi.org/10.3390/ijms25073832

[30] Elshaer, A., Chascsa, D.M.H. and Lizaola-Mayo, B.C. (2024) Exploring Varied Treatment Strategies for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). *Life*, **14**, Article 844. https://doi.org/10.3390/life14070844

[31] Zhu, Y., Xu, J., Zhang, D., Mu, X., Shi, Y., Chen, S., *et al*. (2021) Efficacy and Safety of GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology*, **12**, Article 769069. https://doi.org/10.3389/fendo.2021.769069

[32] Liu, J., Kang, R. and Tang, D. (2021) Signaling Pathways and Defense Mechanisms of Ferroptosis. *The FEBS Journal*, **289**, 7038-7050. https://doi.org/10.1111/febs.16059

[33] Kalavalapalli, S., Bril, F., Guingab, J., Vergara, A., Garrett, T.J., Sunny, N.E., *et al*. (2019) Impact of Exenatide on Mitochondrial Lipid Metabolism in Mice with Nonalcoholic Steatohepatitis. *Journal of Endocrinology*, **241**, 293-305. https://doi.org/10.1530/joe-19-0007

[34] Zhao, Y., Chen, L., Huang, L., Li, Y., Yang, C., Zhu, Y., *et al*. (2022) Cardiovascular Protective Effects of GLP-1: A Focus on the MAPK Signaling Pathway. *Biochemistry and Cell Biology*, **100**, 9-16. https://doi.org/10.1139/bcb-2021-0365

[35] Delrue, C. and Speeckaert, M.M. (2024) Mechanistic Pathways and Clinical Implications of GLP-1 Receptor Agonists in Type 1 Diabetes Management. *International Journal of Molecular Sciences*, **25**, Article 9351. https://doi.org/10.3390/ijms25179351

[36] Okamoto, A., Yokokawa, H., Nagamine, T., Fukuda, H., Hisaoka, T. and Naito, T. (2021) Efficacy and Safety of Semaglutide in Glycemic Control, Body Weight Management, Lipid Profiles and Other Biomarkers among Obese Type 2 Diabetes Patients Initiated or Switched to Semaglutide from Other GLP-1 Receptor Agonists. *Journal of Diabetes & Metabolic Disorders*, **20**, 2121-2128. https://doi.org/10.1007/s40200-021-00899-9

[37] Shang, R. and Miao, J. (2023) Mechanisms and Effects of Metformin on Skeletal Muscle Disorders. *Frontiers in Neurology*, **14**, Article 1275266. https://doi.org/10.3389/fneur.2023.1275266

[38] Meloni, A.R., DeYoung, M.B., Lowe, C. and Parkes, D.G. (2012) GLP-1 Receptor Activated Insulin Secretion from Pancreatic β-Cells: Mechanism and Glucose Dependence. *Diabetes, Obesity and Metabolism*, **15**, 15-27. https://doi.org/10.1111/j.1463-1326.2012.01663.x

[39] Guo, C., Huang, T., Chen, A., Chen, X., Wang, L., Shen, F., *et al*. (2016) Glucagon-Like Peptide 1 Improves Insulin Resistance *in Vitro* through Anti-Inflammation of Macrophages. *Brazilian Journal of Medical and Biological Research*, **49**, e5826. https://doi.org/10.1590/1414-431x20165826

[40] Liu, J., Yang, K., Yang, J., Xiao, W., Le, Y., Yu, F., *et al*. (2019) Liver-Derived Fibroblast Growth Factor 21 Mediates Effects of Glucagon-Like Peptide-1 in Attenuating Hepatic Glucose Output. *EBioMedicine*, **41**, 73-84. https://doi.org/10.1016/j.ebiom.2019.02.037

[41] Gao, H., Song, Z., Zhao, Q., Wu, Y., Tang, S., Alahdal, M., *et al*. (2018) Pharmacological Effects of EGLP-1, a Novel Analog of Glucagon-Like Peptide-1, on Carbohydrate and Lipid Metabolism. *Cellular Physiology and Biochemistry*, **48**, 1112-1122. https://doi.org/10.1159/000491978

[42] Ackeifi, C., Wang, P., Karakose, E., Manning Fox, J.E., González, B.J., Liu, H., *et al*. (2020) GLP-1 Receptor Agonists Synergize with DYRK1A Inhibitors to Potentiate Functional Human B Cell Regeneration. *Science Translational Medicine*, **12**, eaaw9996. https://doi.org/10.1126/scitranslmed.aaw9996

[43] Nguyen, M., Asgharpour, A., Dixon, D.L., Sanyal, A.J. and Mehta, A. (2024) Emerging Therapies for MASLD and Their Impact on Plasma Lipids. *American Journal of Preventive Cardiology*, **17**, Article 100638. https://doi.org/10.1016/j.ajpc.2024.100638

[44] 中华医学会肝病学分会. 代谢相关(非酒精性)脂肪性肝病防治指南(2024 年版) [J]. 中华肝脏病杂志, 2024, 32(5): 418-434.

[45] Lara-Romero, C. and Romero-Gómez, M. (2024) Treatment Options and Continuity of Care in Metabolic-Associated Fatty Liver Disease: A Multidisciplinary Approach. *European Cardiology Review*, **19**, e06. https://doi.org/10.15420/ecr.2023.34

[46] Tan, H.C., Dampil, O.A. and Marquez, M.M. (2022) Efficacy and Safety of Semaglutide for Weight Loss in Obesity without Diabetes: A Systematic Review and Meta-Analysis. *Journal of the ASEAN Federation of Endocrine Societies*, **37**, 65-72. https://doi.org/10.15605/jafes.037.02.14

[47] Feng, X., Zhang, R., Yang, Z., Zhang, K. and Xing, J. (2024) Mechanism of Metabolic Dysfunction-Associated Steatotic Liver Disease: Important Role of Lipid Metabolism. *Journal of Clinical and Translational Hepatology*, **12**, 815-826. https://doi.org/10.14218/jcth.2024.00019

[48] Bjerre Knudsen, L., Madsen, L.W., Andersen, S., Almholt, K., de Boer, A.S., Drucker, D.J., *et al*. (2010) Glucagon-Like Peptide-1 Receptor Agonists Activate Rodent Thyroid C-Cells Causing Calcitonin Release and C-Cell Proliferation. *Endocrinology*, **151**, 1473-1486. https://doi.org/10.1210/en.2009-1272

[49] Sun, Y., Liu, Y., Dian, Y., Zeng, F., Deng, G. and Lei, S. (2024) Association of Glucagon-Like Peptide-1 Receptor Agonists with Risk of Cancers-Evidence from a Drug Target Mendelian Randomization and Clinical Trials. *International Journal of Surgery*, **110**, 4688-4694. https://doi.org/10.1097/js9.0000000000001514

[50] Manuel, S.L., Lin, F. and Kutty, S.M. (2023) An Atypical Presentation of Dulaglutide-Induced Pancreatitis Complicated by Superior Mesenteric Vein Thrombosis. *Cureus*, **15**, e50051. https://doi.org/10.7759/cureus.50051

[51] Zhu, Y., Xu, J., Zhang, D., Mu, X., Shi, Y., Chen, S., *et al*. (2021) Efficacy and Safety of GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Mellitus and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology*, **12**, Article 769069. https://doi.org/10.3389/fendo.2021.769069

[52] Lyu, B., Hwang, Y.J., Selvin, E., Jameson, B.C., Chang, A.R., Grams, M.E., *et al*. (2023) Glucose-Lowering Agents and the Risk of Hypoglycemia: A Real-World Study. *Journal of General Internal Medicine*, **38**, 107-114. https://doi.org/10.1007/s11606-022-07726-8

[53] Yabut, J.M. and Drucker, D.J. (2022) Glucagon-Like Peptide-1 Receptor-Based Therapeutics for Metabolic Liver Disease. *Endocrine Reviews*, **44**, 14-32. https://doi.org/10.1210/endrev/bnac018

[54] Kumarathurai, P., Anholm, C., Larsen, B.S., Olsen, R.H., Madsbad, S., Kristiansen, O., *et al*. (2016) Effects of Liraglutide on Heart Rate and Heart Rate Variability: A Randomized, Double-Blind, Placebo-Controlled Crossover Study. *Diabetes Care*, **40**, 117-124. https://doi.org/10.2337/dc16-1580

[55] Romera, I., Cebrián-Cuenca, A., Álvarez-Guisasola, F., Gomez-Peralta, F. and Reviriego, J. (2019) A Review of Practical Issues on the Use of Glucagon-Like Peptide-1 Receptor Agonists for the Management of Type 2 Diabetes. *Diabetes Therapy*, **10**, 5-19. https://doi.org/10.1007/s13300-018-0535-9

[56] Smits, M.M., van Raalte, D.H., Tonneijck, L., Muskiet, M.H.A., Kramer, M.H.H. and Cahen, D.L. (2016) GLP-1 Based Therapies: Clinical Implications for Gastroenterologists. *Gut*, **65**, 702-711. https://doi.org/10.1136/gutjnl-2015-310572

[57] Begum, F., Chang, K., Kapoor, K., Vij, R., Phadke, G., Hiser, W.M., *et al*. (2024) Semaglutide-Associated Kidney Injury. *Clinical Kidney Journal*, **17**, sfae250. https://doi.org/10.1093/ckj/sfae250

[58] Smits, M.M. and Van Raalte, D.H. (2021) Safety of Semaglutide. *Frontiers in Endocrinology*, **12**, Article 645563. https://doi.org/10.3389/fendo.2021.645563

[59] Huynh, D. (2023) Dual Metformin and Glucagon-Like Peptide-1 Receptor Agonist Therapy Reduces Mortality and Hepatic Complications in Cirrhotic Patients with Diabetes Mellitus. *Annals of Gastroenterology*, **36**, 555-563. https://doi.org/10.20524/aog.2023.0814