

· 综述 ·

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他汀类药物在代谢相关脂肪性肝病治疗中的应用

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摘要: 代谢相关脂肪性肝病(MAFLD)及其进展形式——代谢相关性脂肪性肝炎(MASH)已成为全球慢性肝病的主要病因,其发病率持续上升,与肥胖、2型糖尿病等代谢紊乱密切相关。MAFLD的核心发病机制涉及胰岛素抵抗、脂代谢异常及慢性炎症反应,可进展为MASH,导致肝纤维化、肝硬化甚至肝细胞癌。目前,针对MAFLD的有效药物治疗仍有限。本文基于PRISMA指南,系统综述他汀类药物在MAFLD治疗中的作用。研究表明,他汀类药物不仅能改善血脂谱和肝酶水平,还对合并心血管疾病或2型糖尿病等患者具有良好获益,且长期使用还可以降低肝细胞癌风险。然而,其潜在的肝毒性及肌病风险需警惕,因此临床应个体化用药并定期监测肝功能。

关键词: 羟甲基戊二酰基 CoA 还原酶抑制剂; 代谢相关脂肪性肝病; 治疗学

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Application of statins in the treatment of metabolic dysfunction-associated fatty liver disease

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Abstract: Metabolic dysfunction-associated fatty liver disease (MAFLD) and its progressive form metabolic dysfunction-associated steatohepatitis (MASH) have become the leading causes of chronic liver diseases worldwide, and the incidence rate of MAFLD continues to rise, which is closely associated with metabolic disorders such as obesity and type 2 diabetes. The core pathogenesis of MAFLD involves insulin resistance, abnormal lipid metabolism, and chronic inflammation, which can progress to MASH and lead to liver fibrosis, liver cirrhosis, and even hepatocellular carcinoma (HCC). At present, there are still limited effective pharmacotherapies for MAFLD. Based on the PRISMA guidelines, this article systematically reviews the role of statins in MAFLD. Studies have shown that statins not only improve blood lipid profiles and the levels of liver enzyme, but also bring good benefits to patients comorbid with cardiovascular disease or type 2 diabetes, and long-term use can also reduce the risk of HCC. However, the potential risks of hepatotoxicity and myopathy should be taken seriously, which, therefore, requires individualized medication and regular monitoring of liver function in clinical practice.

Key words: Hydroxymethylglutaryl-CoA Reductase Inhibitors; Metabolic Dysfunction-Associated Fatty Liver Disease; Therapeutics

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代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD)现已成为全球患病率第2位的肝脏疾病,预计将成为未来肝移植的主要原因。MAFLD是一种由营养过剩和胰岛素抵抗(insulin resistance, IR)引发的慢性肝病,其病理特征为肝脏脂肪含量>5%,常见于肥胖、代谢综合征及2型糖尿病(type 2 diabetes mellitus, T2DM)患者。该疾病可进展为代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis, MASH),导致肝纤维化、肝硬化,甚至肝细胞癌(hepatocellular carcinoma, HCC)^[1-2]。目前,MAFLD的治疗以生活方式干预为主,尚无特效药物^[2]。2024年相关指南明确支持他汀类药物用于MAFLD治疗^[2],但临床实施仍受限于转氨酶升高的潜在风险。本文基于PRISMA指南,系统综述他汀类药物治疗MAFLD的作用机制、临床应用及安全性,以期对相关研究和实践提供参考。

1 他汀类药物治疗MAFLD的作用机制

IR是MAFLD发病的核心机制,其通过抑制脂肪分解,增加游离脂肪酸(free fatty acid, FFA)向肝脏的输送,导致肝脏脂质堆积。过量的FFA可诱发线粒体功能障碍和内质网应激,导致活性氧(reactive oxygen species, ROS)堆积,进而激活白细胞介素1 β (interleukin-1 β , IL-1 β)、肿瘤坏死因子 α (tumor necrosis factor, TNF- α)等促炎因子,加重肝脏炎症反应^[3]。此外,MAFLD的发病与肠道屏障损伤密切相关。肠道菌群失调通过破坏肠上皮屏障,使内毒素和细菌代谢产物易位至肝脏,激活肝内巨噬细胞并促进炎症反应,形成肠-肝轴恶性循环,加速MAFLD的疾病进展^[4]。同时,肠道菌群代谢产物也会影响氧化应激和脂质代谢过程,从而进一步加重肝损伤^[4-5]。

炎性小体是炎症的主要因素,是激活胱天蛋白酶1(cysteine aspartic acid specific protease-1, caspase-1)的大型多蛋白复合物,可通过细胞内NOD样受体感知外源性和内源性危险信号。核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3(nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3, NLRP3)炎性小体是一种重要的免疫反应通路,是MAFLD治疗的重要靶点^[6]。肝脏脂肪积聚是MAFLD的核心特征,特别是FFA的过量堆积通过双重机制激活NLRP3炎性小体:一方面,过量的FFA会引发肝细胞内的氧化应激反应,增加ROS的生成,导致线粒体功能异常和膜通透性的改变^[4,7];另一方面,FFA代谢产物可直接激活NLRP3炎性小体^[7-8]。二者协同触发NLRP3炎性小体

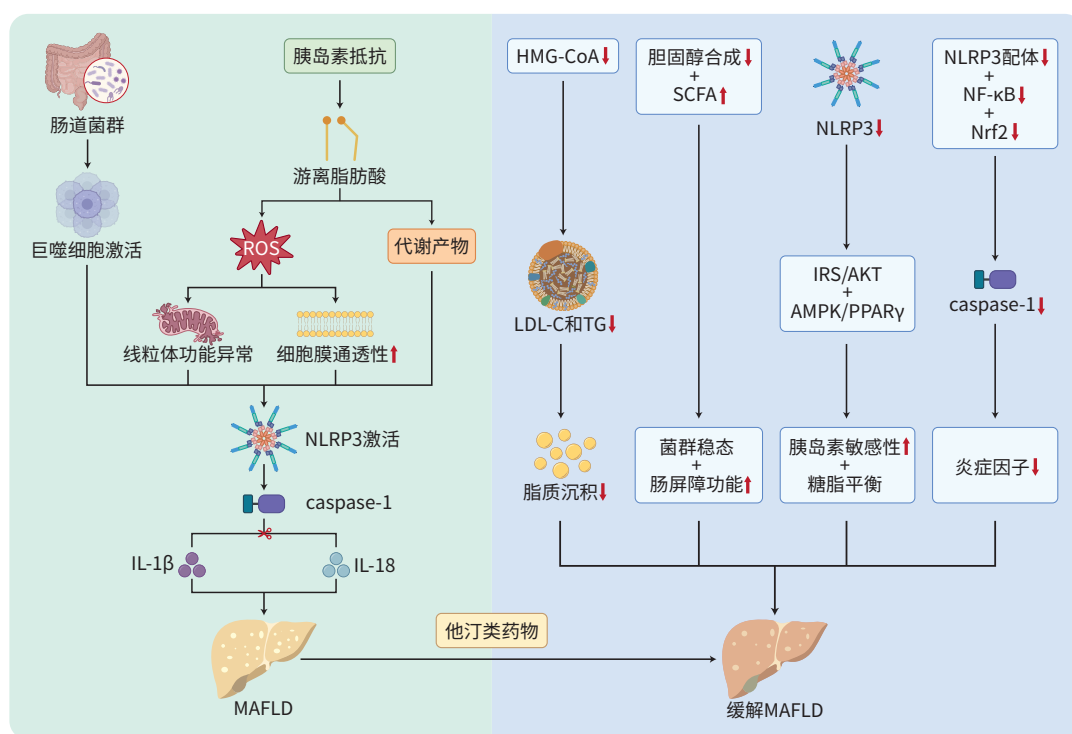
的激活,进一步启动包含caspase-1在内的信号级联反应,通过caspase-1的裂解作用为炎症细胞因子提供正反馈刺激,蛋白水解激活细胞因子IL-1 β 和白细胞介素18(interleukin-18, IL-18),引发局部和全身性的炎症反应^[6]。此外,激活的NLRP3炎性小体释放的IL-1 β 和IL-18,可阻断胰岛素受体底物/蛋白激酶B信号通路,导致肝细胞的IR,抑制葡萄糖摄取,从而驱动肝损伤进程^[9]。在肝脏中,这种持续的炎症反应不仅加剧了MAFLD的病理进程,还可能引发肝纤维化、肝硬化甚至HCC的发生。肠道菌群紊乱通过破坏肠屏障致脂多糖入肝,激活肝巨噬细胞的Toll样受体4/核因子 κ B信号,启动NLRP3炎性小体并释放IL-1 β 和IL-18,驱动肝内炎症反应与脂肪变性,形成肠-肝轴恶性循环^[10]。

他汀类药物作为羟基甲基戊二酰辅酶A(hydroxymethylglutaryl-CoA, HMG-CoA)还原酶抑制剂,可以通过多靶点机制改善MAFLD(图1):(1)抑制HMG-CoA还原酶阻断胆固醇合成,降低血清低密度脂蛋白胆固醇与甘油三酯的水平,直接减轻肝脏脂质沉积与脂毒性,改善脂肪变性;(2)减少NLRP3炎性小体形成,下调核因子 κ B信号通路以抑制促炎因子转录,激活核因子 κ B信号通路以清除ROS,三者协同下调炎症反应,减少caspase-1的活化及IL-1 β 的成熟释放,并降低TNF- α 等促炎因子的表达^[11];(3)抑制胆固醇合成改变胆汁酸,减轻肠道炎症,同时促进产短链脂肪酸菌增殖,双向重塑菌群稳态与肠屏障功能^[5,12];(4)通过抑制NLRP3炎症反应以恢复胰岛素受体底物/蛋白激酶B信号通路,并调节肠道菌群-短链脂肪酸轴激活AMP活化的蛋白质激酶/过氧化物酶体增殖物激活受体 γ 信号通路促进脂质代谢,同时刺激胰高血糖素样肽1分泌,协同提升胰岛素敏感性与糖脂代谢平衡^[5,13]。这种多靶点协同作用使他汀类药物能有效减轻肝脏脂肪变性、抑制炎症反应并延缓纤维化进展,为MAFLD的治疗提供了新的策略。

2 他汀类药物治疗MAFLD的药物代谢动力学特征

他汀类药物治疗MAFLD的药物代谢动力学特征主要表现为肝脏首过效应、肝脏高分布性、细胞色素P450(cytochrome P450, CYP450)3A4酶(CYP3A4)代谢和半衰期等。

他汀类药物经口服吸收后,其中亲脂性他汀类药物易进入细胞并与细胞膜相互作用以抑制HMG-CoA还原酶,亲水性他汀类药物则具有肝脏高选择性^[14-15]。亲水性他汀类药物的肝脏高选择性可以增强其对肝脏的靶



注:ROS,活性氧;NLRP3,核苷酸结合寡聚结构域样受体家族热蛋白结构域相关蛋白3;caspase-1,胱天蛋白酶1;IL-1 β ,白细胞介素1 β ;IL-18,白细胞介素18;MAFLD,代谢相关脂肪性肝病;HMG-CoA,羟甲基戊二酰辅酶A;SCFA,短链脂肪酸;NF- κ B,核因子 κ B;Nrf2,核因子红系2相关因子2;IRS,胰岛素受体底物;AMPK,AMP活化的蛋白质激酶;PPAR γ ,过氧化物酶体增殖物激活受体 γ ;LDL-C,低密度脂蛋白胆固醇;TG,甘油三酯。

图1 他汀类药物治疗MAFLD的作用机制

Figure 1 The mechanism of action of statins in the treatment of MAFLD

向降脂作用。此外,肝脏中富含HMG-CoA还原酶,亲脂性他汀类药物在肝脏中能够有效抑制该酶活性,减慢肝细胞内胆固醇的合成速率,从而有效降低机体血脂水平。CYP3A4是肝脏和肠道中最丰富的药物代谢细胞色素P50酶,参与30%以上的药物代谢。亲脂性他汀类药物可通过肝脏CYP3A4代谢生成活性代谢产物^[15],协同增强其降脂效果并延长作用时间。

他汀类药物全身生物利用度较低,但肝脏首过效应显著,且具有显著的肝脏靶向分布特性,这种分布特征与其高达90%的血浆蛋白结合率共同作用,使得药物能在肝脏中维持稳定的有效浓度^[15]。此外,部分他汀类药物半衰期可达20 h以上^[14]。这种独特的药代动力学特征确保了药物在肝脏中持续发挥降脂作用,为MAFLD患者的临床治疗提供了稳定的药效学基础。

3 他汀类药物治疗MAFLD的研究进展

3.1 他汀类药物治疗MAFLD的随机对照试验(randomized controlled trial, RCT) 早期研究评估发现他汀类药物联合抗氧化剂可降低MAFLD风险,但因联

合用药的局限性,难以确定他汀类药物的单独疗效^[16]。值得注意的是,后期研究发现他汀类药物单药治疗与联合抗氧化剂在改善血清酶学和抗氧化指标方面效果相当,提示其作为独立治疗方案的可行性^[17]。有研究单独使用常规剂量的他汀类药物可安全、有效地降低MAFLD患者的肝酶浓度、减轻肝脂肪变性^[18]。大规模临床观察表明,即使长期使用,他汀类药物仍保持良好安全性,能有效改善疾病状态^[19]。

一项包含14项研究的荟萃分析表明,他汀类药物不仅能改善患者肝酶水平和肝组织学,还可降低健康人群中MAFLD的发病风险^[20]。另一项纳入19项RCT的荟萃分析进一步证实其对肝酶和血脂指标的改善作用^[21]。总体而言,上述临床证据为他汀类药物在MAFLD治疗中的应用提供了重要依据。

3.2 他汀类药物治疗MAFLD的动物试验 动物模型研究对于阐明他汀类药物对肝组织学的影响机制具有重要补充价值。多项动物实验表明,他汀类药物的使用可改善小鼠的肝脂肪变性、炎症及纤维化。机制研究表明,他汀类药物可以通过抑制NLRP3炎性小体的激活、

抑制CD8⁺T细胞的浸润、增强胰高血糖素诱导的肝细胞葡萄糖输出、下调氧化和晚期脂氧化终末产物-晚期糖基化终末产物受体通路应激、减少胆汁酸血浆浓度、下调顶端钠依赖性胆汁酸转运体等多靶点调节微循环和实现脂质代谢重编程,进而改善MAFLD^[22-26]。另有研究表明,不同剂量他汀类药物在高脂饮食诱导的MAFLD模型中均显示出保护作用:常规剂量可改善血脂水平并减少MAFLD相关并发症^[27];中等剂量给药在减少小叶炎症和肝细胞气球样变方面效果尤为显著^[28];高剂量给药可以明显降低血脂水平,且肝酶未见明显升高^[29]。上述实验从多个角度证实了他汀类药物改善肝脂肪变性和炎症反应的有效性,为其临床应用提供了坚实的实验基础。

3.3 他汀类药物治疗MAFLD的二次研究 二次研究可系统整合多项原始数据,提升结论的可靠性与普适性,有助于弥补单一RCT研究的局限性。

在肝脏活组织检查证实的MAFLD患者中,他汀类药物的使用与MASH发生率呈负相关,提示其可能具有肝保护作用^[30]。多项研究均表明,他汀类药物不仅能改善肝脂肪变性和纤维化程度,还能显著降低MAFLD的发病风险^[30-32]。特别值得注意的是,良好的用药依从性与MAFLD风险降低直接相关^[33]。中高剂量他汀类药物可延缓肝纤维化进展^[34],常规剂量即可安全有效地改善肝功能指标^[31],从而降低全因死亡率和肝脏不良事件风险^[35]。

MAFLD作为HCC的重要独立危险因素,其患者尤其是MAFLD型肝硬化患者的HCC发生风险显著增高。他汀类药物在MAFLD患者防止病毒复制、增强抗病毒治疗及刺激抗肿瘤免疫等方面具有显著效果^[36],可将HCC发展的风险降低46%^[37],尤其对65岁以下人群效果更优^[38]。上述研究结果为他汀类药物在MAFLD患者中的临床应用提供了有力证据,特别是在改善代谢异常、延缓疾病进展和预防HCC方面具有重要价值。

4 他汀类药物的MAFLD特殊人群应用与临床安全性特征

研究表明,他汀类药物对MAFLD患者具有安全性,并能降低病死率、肝功能失代偿及HCC风险。然而,因担忧肝毒性,他汀类药物处方不足40%~50%^[32]。值得注意的是,T2DM、心血管疾病(cardiovascular disease,CVD)等合并症会进一步增加MAFLD患病风险,还会进一步升高HCC发生率。因此,他汀类药物在MAFLD的特定人群

中的疗效仍需更多研究验证。

4.1 他汀类药物在MAFLD的特殊人群中的应用

4.1.1 T2DM 糖代谢异常是MAFLD的重要危险因素,T2DM患者中MAFLD发病率高达65.0%^[2,39]。在经活组织检查证实的MAFLD合并糖尿病前期或T2DM患者中,他汀类药物表现出良好的安全性,不仅能防止脂肪性肝炎和纤维化的发生,还可降低其心血管事件的发生风险,因此鼓励该类人群接受他汀类药物的治疗^[40-42]。他汀类药物在大部分T2DM患者的治疗中是必需的,临床研究证据表明,他汀类药物可以降低T2DM患者MAFLD/MASH的发生率,并对已发生MAFLD相关失代偿性肝硬化的T2DM患者也具有保护作用,且存在剂量反应关系^[43-44]。此外,他汀类药物尤其可以显著降低女性和年轻MAFLD合并T2DM患者的肝纤维化、肝硬化患病率^[45]。

4.1.2 CVD 除MAFLD的严重肝病并发症外,CVD是MAFLD患者死亡的主要原因^[46]。研究表明,MAFLD是CVD的早期预警指标,可使冠心病风险增加1.33倍,主要不良心血管事件风险增加1.45倍^[2]。他汀类药物通常可以安全有效地减轻MAFLD患者群体的动脉粥样硬化性CVD负担^[47],临床指南推荐将他汀类药物用于高危血脂患者的心血管一级和二级预防^[48]。根据脂肪肝指数(fatty liver index,FLI),他汀类药物治疗可降低高FLI(≥ 60)个体的CVD风险,且大部分MAFLD(FLI ≥ 60)患者符合降脂治疗指征^[49]。临床证据表明,他汀类药物不仅能改善MAFLD,还可作为CVD一级预防方案,显著降低CVD发病率和病死率^[46,48-49]。动物实验进一步证实,他汀类药物可同时减轻肝脂肪变性和CVD风险^[50],并能减轻肝脏炎症、抑制肝星状细胞的活化以及改善肝窦内皮细胞功能障碍^[45]。他汀类药物的心血管保护作用远超其潜在副作用^[51],且持续用药患者的CVD事件发生率及病死率均显著低于停药者^[52]。上述证据均支持他汀类药物在MAFLD合并CVD患者中的临床应用价值。

4.1.3 妊娠期 虽然他汀类药物可通过改善血管功能用于子痫前期防治,但妊娠期MAFLD患者使用他汀类药物存在显著争议。MAFLD孕妇可能出现先兆子痫、早产、新生儿黄疸等不良妊娠结局,并可能增加儿童代谢综合征和儿童MAFLD的风险^[53]。目前,他汀类药物因潜在致畸性仍被视为妊娠禁忌。但通过交互式评价发现,他汀类药物与胎儿畸形的发生无关,其使用可能有助于预防不良心血管结局,有可能减少氧化应激和血管生成功能障碍,其中亲水性他汀类药物,例如普伐他

汀,在妊娠期使用更安全^[54]。有研究表明,在妊娠期间使用他汀类药物不会增加胎儿先天性异常的风险,而对于患有血脂异常或高危的女性,以及受孕前使用他汀类药物的女性,他汀类药物可以持续使用,亦不会增加新生儿不良反应的风险^[55]。但鉴于缺乏临床原始证据,建议妊娠期 MAFLD 患者首选医学营养治疗和生活方式干预,仅在获益明确超过风险时谨慎考虑他汀类药物治疗,并需充分评估风险和知情同意^[56]。

4.1.4 老年人群 现阶段 MAFLD 老年人口发病率呈上升趋势,尤其是 65 岁以上人群 MAFLD 患病率显著增高,且老年患者常合并 CVD、T2DM 等高危因素,因此老年患者表现出更严重的生化、血液学和组织学变化^[57]。前瞻性研究证实,老年患者使用他汀类药物总体安全,但对于有慢性肝病或酗酒史的患者,需慎重服用并定期监测肝功能^[58]。此外,他汀类药物对 75 岁及以上的高胆固醇血症老年患者还有益于 CVD 和全因死亡率的一级预防,而不会增加重大不良事件的风险,如肌病和肝功能障碍等^[59]。

4.2 他汀类药物临床安全性特征 他汀类药物总体上具有良好的安全性,引起的肝损伤通常为—过性,转氨酶轻度升高(<3 倍正常值上限)且无其他肝损伤时无需停药^[60-61]。但仍存在需警惕高危人群的不良反应。剂量相关性肌病是最常见的不良反应,通常在停药后缓解^[62],但因老年患者肌肉质量和药物代谢酶随年龄增长而下降,其肌肉症状风险显著增加^[63]。横纹肌溶解是最严重的肌肉并发症,其中亲脂性他汀类药物风险显著高于亲水性他汀类药物,特别是在接受亲脂性他汀类药物高剂量治疗或已经出现全身肌肉功能障碍的患者中,并且男性更易受到他汀类药物肌毒性的影响^[64]。亲脂类他汀类药物更易透过血脑屏障,通过抑制神经细胞胆固醇合成导致认知功能障碍,且这种风险随年龄增长而加剧^[65],老年患者(>65 岁)主要出现肌痛和头晕,而 18~64 岁患者更易发生失眠和乏力^[66]。

他汀类药物相关的肝损伤主要表现为肝酶升高,其机制与肝细胞和胆汁淤积损伤相关,常见于大剂量用药、联合其他降脂药物或细胞色素 P450 酶途径药物,以及老年或肝肾功能损害患者^[67]。除不遵守他汀类药物戒断以外,多数肝损伤是可逆的,仅需停药即可恢复^[60-61,68],他汀类药物引起的具有临床意义的药物性肝损伤非常罕见,极少数病例出现严重肝衰竭,甚至死亡^[60,69]。因此,尽管他汀类药物总体安全性较好,但对急性肝病、失代偿性肝病或有药物性肝损伤病史的患者应谨慎使用。

5 小结

他汀类药物在延缓肝病进展、降低门静脉压力和延长代偿期肝硬化患者的生存期等方面显示出良好前景^[1],但其潜在的肝损伤和严重肌病风险仍需警惕。临床应用时需综合评估患者肝肾功能,对肝损伤、严重肌肉反应以及肝肾功能问题的高危人群应谨慎选择治疗方案,同时密切监测肝酶和肌酸激酶水平以早期识别不良反应。对于代谢异常和心血管疾病高危患者,他汀类药物可能带来显著获益,但需充分考虑药物相互作用因素。治疗决策应基于个体化风险评估,结合患者完整病史制订方案,并配合饮食控制和运动等生活方式干预。目前仍需大规模长期临床研究进一步明确他汀类药物的最佳用药方案、确切作用机制以及对 MAFLD 转归的长期影响,从而更精准地指导临床实践。

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