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· 综述与讲座 ·

# 代谢功能障碍相关脂肪性肝病相关临床不良影响

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[摘要]　代谢功能障碍相关脂肪性肝病(MASLD)旧称非酒精性脂肪性肝病(NAFLD),是最常见的肝脏疾病,全球患病率超过 30%。MASLD 不仅会导致肝脏相关疾病的发病率和死亡率增加,近年来研究表明,MASLD 在疾病进程中还会累及全身多个系统。相关疾病谱包括心血管疾病、2 型糖尿病、代谢综合征、慢性肾脏病(CKD)、肝外恶性肿瘤、肌少症、尿石症等。这些肝外疾病的严重程度与 MASLD 的严重程度密切相关。全面认识和了解 MASLD 与这些疾病之间的相互关系对及时的筛查、诊断及启动多学科管理至关重要。本文对已发表的研究和文献进行了系统回顾,旨在全面分析 MASLD 的临床不良影响,包括对肝脏及心血管、糖代谢、肾脏等多系统/器官组织的影响。

[关键词]　代谢功能障碍相关脂肪性肝病;　肝癌;　心血管疾病;　糖尿病;　慢性肾脏病;　恶性肿瘤

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代谢功能障碍相关脂肪性肝病(MASLD)旧称非酒精性脂肪性肝病(NAFLD),是最常见的肝脏疾病,全球患病率超过 30%[1-2]。长期以来,MASLD 一直被认为是一种肝脏疾病。但近年来的研究逐步揭示了 MASLD 对心血管、糖代谢、肾脏、肝外恶性肿瘤等多系统/器官组织的显著影响[3-6]。这些靶器官/系统在代谢调节中发挥至关重要的作用,且通常对 MASLD 相关的代谢紊乱(如胰岛素抵抗、血脂异常、高血压等)有明显易感性[7-9]。MASLD 病理过程中的炎症和纤维化进程会对这些器官系统产生显著影响,包括心血管功能障碍、肾脏损害、糖代谢异常等,显著增加了相关疾病的发病率和死亡率,进而影响患者的预后[8,10]。MASLD 的系统损害很大程度上归因于 MASLD 的代谢失调,包括肥胖、胰岛素抵抗、炎症反应、脂质代谢异常等,其可在心血管、肌肉、肾脏、糖代谢、肝外恶性肿瘤等并发症中发挥关键作用[11-12]。

## 一、肝脏并发症

MASLD 患者肝纤维化[13]、肝癌的风险明显增加。Kanwal 等[14]比较了近 60 万例 MASLD 组患者及其匹配的对照,随访期间发现 MASLD 患者肝癌的发生率显著高于对照组,其中肝硬化的 MASLD 患者肝癌的年发病率最高。多项基于人群的流行病学研究结果显示,MASLD 相关肝癌的发病率呈逐年上升趋势;相关模型预测显示,到 2030 年,美国、法国和我国 MASLD 相关肝癌的年发病例数将分别增加 137%、117% 和

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86%[15-16]。与酒精性肝病和病毒性肝炎相关肝癌不同的是,MASLD 相关肝癌可发生于非肝硬化的患者中[17-18]。高龄[19]、肥胖[19]、2 型糖尿病[20]、晚期肝纤维化或肝硬化[14,21]是 MASLD 患者发生肝癌的主要危险因素。肠道菌群失调[22]、*PNPLA3* 等基因的遗传多态性[23]也可能参与了 MASLD 患者肝癌的发病过程。

虽然无论有无肝纤维化,MASLD 均可发展为肝癌,但肝纤维化会明显增加这种风险。肝纤维化是 MASLD 患者发生肝癌最重要的危险因素。日本一项全国性调查结果显示,糖尿病患者肝癌的年发病率为 0.11%,但当肝纤维化指数≥3.5 时,肝癌的年发病率上升至 1.0%[24]。另外一项大型回顾性队列研究结果显示,合并肝硬化和未合并肝硬化的 MASLD 患者肝癌的发病率分别为 10.6/1 000 人年、0.08/1 000 人年,提示合并肝硬化使 MASLD 患者肝癌的发生风险增加了 10 倍以上[14]。

## 二、心血管疾病

MASLD 是心血管疾病的独立危险因素,MASLD 患者心血管疾病的发病率和死亡率均显著增加[7,25-27]。Mantovani 等[28]对 36 项关于 MASLD 与心血管疾病的纵向研究进行了 Meta 分析,共纳入不同国家不同地区的 580 万例患者,中位随访时间 6.5 年;随访期间共发生近 10 万例致死性或非致死性心血管事件。该研究分析结果显示,MASLD 与致死性或非致死性心血管事件风险增加有关(*HR* = 1.45,95% *CI* 1.31 ~ 1.61),且随着肝脏疾病的进展,这一风险会进一步增加。特别是肝纤维化阶段,心血管事件的风险显著增加(*HR* = 2.5,95% *CI* 1.68 ~ 3.72)。Lee 等[29]利用韩国的全国健康筛查数据库对近 900 万例 MASLD 患者进行了随访,中位随访时间 12.3 年,结果显示 MASLD 与心血管事件发生风险增加明显相关(*HR* = 1.43,95% *CI* 1.41 ~ 1.45)。日本的一项纳入 245 万例 MASLD 患者的回顾性研究显示,患者心血管疾病的发病率显著增加,*HR* = 2.69(95% *CI* 2.55 ~ 2.83);且其糖尿病和高甘油三酯血症的发病率也明显增加,这可能是影响心血管疾病发生发展的原因之一[30]。Liang 等[31]对上海市 6 873 例研究对象进行了持续 4.6 年的随访,结果显示 MASLD 患者发生心血管事件的风险明显增加(*HR* = 1.44,95% *CI* 1.15 ~ 1.81)。

此外,还有研究结果显示,MASLD 与某些心律失常的发生风险有明显相关性[32]。在对 9 项观察性研究(包括 5 项横断面研究和 4 项纵向研究)的 Meta 分析结果中显示,MASLD 与房颤风险增加明显相关(*OR* = 2.07,95% *CI* 1.38 ~ 3.10),且独立于房颤的常见危险因素(年龄、性别、BMI、高血压等)[33]。

多项研究表明,胰岛素抵抗、糖代谢紊乱、炎症反应、内皮功能障碍、内脏脂肪沉积、氧化应激等同时与 MASLD 和心血管疾病的发生和发展密切相关,这可能是 MASLD 患者心血管疾病高发的重要原因[29,34-35]。胰岛素抵抗会导致脂肪组织产生的脂联素等脂肪因子减少,活性氧生成增加,进而导致游离脂肪酸氧化、甘油三酯累积、脂肪生成增加,还会促进炎症反应,最终加速动脉粥样硬化斑块的形成和进展,导致 MASLD 患者心血管疾病风险增加[36-37]。

## 三、代谢综合征和 2 型糖尿病

从 NAFLD 到 MASLD 的名称更迭强调了代谢障碍在疾病进程中的重要作用。MASLD 的发病率与肥胖的患病率呈现相似的上升趋势[38]。有研究显示,超过 90% 接受减重手术的肥胖症患者合并 MASLD[38]。肥胖 MASLD 患者的血压、胰岛素抵抗、糖化血红蛋白、转氨酶、肌酐水平均明显高于非肥胖的 MASLD 患者[39]。但也有部分 MASLD 患者 BMI 处于正常范围。BMI 正常 MASLD 的发病人数不断增加。有研究表明,BMI 正常 MASLD 患者的累积心血管事件发病率高于超重/肥胖 MASLD 患者[40],无糖尿病的 BMI 正常 MASLD 患者的全因死亡风险(*HR* = 2.34)高于无糖尿病的超重/肥胖 MASLD 患者(*HR* = 1.23)[41]。这些研究结果提示,在 MASLD 发展过程中。BMI 可能难以全面评估患者的代谢状况,这可能是因为 BMI 无法区别脂肪组织和肌肉组织的质量。但由于 BMI 正常 MASLD 患者缺乏其他评估代谢功能的指标,所以 BMI 正常 MASLD 的患病率可能被低估。

多项研究表明,MASLD 与 2 型糖尿病之间存在双向关系,二者互相影响。MASLD 患者 2 型糖尿病的发病率增加。一项纳入亚洲、美国和欧洲共 50 万例研究对象的 Meta 分析结果表明,在调整了年龄、性别、BMI 和其他常规代谢危险因素后,MASLD 与 2 型糖尿病发病风险增加显著相关。并且肝脂肪变性和纤维化程度越重,2 型糖尿病发病风险越高[42]。与此一致,Chung 等[43]利用韩国的全国人群数据库进行的研究结果显示,MASLD 患者发生糖尿病的风险显著高于对照组(校正 *HR* = 4.97,95% *CI* 4.90 ~ 5.05),在男性、吸烟、久坐、超重人群中,这种关联更为显著。MASLD 患者的肝脏脂肪累积导致肝脏胰岛素抵抗,增加肝糖原合成,进一步加重全身胰岛素抵抗和心血管事件风险[44]。

2 型糖尿病又会促进 MASLD 进展为肝硬化,增加肝脏相关死亡风险及全因死亡风险。有研究显示,平

均糖化血红蛋白每增加 1%，肝纤维化加重的几率增加 15%[45]。

## 四、慢性肾脏病

MASLD 与慢性肾脏病（CKD）有许多共同的高危因素，包括腹型肥胖、胰岛素抵抗、血脂异常、高血压等。多项研究表明，MASLD 与 CKD 发病率增加有关，且独立于其他危险因素[42,46-48]。一项纳入 13 项纵向研究、约 120 万例研究对象的 Meta 分析显示，MASLD 与 CKD≥3 期[估算的肾小球滤过率（eGFR）< 60 ml · min$^{-1}$ · (1.73 m$^2$)$^{-1}$，伴或不伴蛋白尿]的风险明显相关，并且独立于年龄、性别、肥胖、高血压、2 型糖尿病等传统的 CKD 风险因素[42]。这项研究还显示，随着肝脏疾病的进展，特别是肝纤维化严重程度加剧，CKD 的风险进一步增加[42]。Wei 等[48]对 3 627 例我国 2 型糖尿病患者进行的纵向研究结果同样显示，即便在调整了年龄、性别、肥胖、高血压、血脂异常、肝酶、基线 eGFR 后，MASLD 仍然与 10 年随访期间 CKD 风险增加有关（*HR* = 1.28，95% *CI* 1.09 ~ 1.50）。

一项纳入 14 000 余例日本成年人、平均随访 6.9 年的队列研究结果显示，在调整吸烟史、肥胖、糖尿病、高血压、血脂异常等其他心血管危险因素后，MASLD 合并 CKD 比单独 MASLD 或 CKD 能更准确地预测缺血性心脏病的风险[49]。

许多研究进一步探讨了 MASLD 与 CKD 风险关联的潜在机制，包括全身胰岛素抵抗、致动脉粥样硬化性血脂异常和高血压、肾素-血管紧张素系统的激活、内皮功能障碍导致的促凝状态和慢性炎症反应等，这些都可能在 MASLD 患者 CKD 的进展中发挥作用[50-53]。此外，还有研究结果表明，某些遗传多态性，特别是 *PNPLA3* 基因等，也可能在 MASLD 患者 CKD 的发病中发挥一定作用[53-55]。

## 五、肝外恶性肿瘤

既往研究表明，肝外恶性肿瘤是 MASLD 患者的主要死因之一[56-57]。韩国一项纳入 25 947 例受试者（其中有 8 721 例 MASLD 患者）的队列研究结果显示，MASLD 患者的恶性肿瘤发病率明显高于非 MASLD 患者（*HR* = 1.32，95% *CI* 1.17 ~ 1.49）[58]。在调整人口统计学和代谢因素后，MASLD 与 3 种恶性肿瘤密切相关：肝细胞癌（*HR* = 16.73，95% *CI* 2.09 ~ 133.85）、男性结直肠癌（*HR* = 2.01，95% *CI* 1.10 ~ 3.68）和女性乳腺癌（*HR* = 1.92，95% *CI* 1.15 ~ 3.20）。Allen 等[59]对一大型社区人群进行了平均 8 年的随访，结果显示 MASLD 患者恶性肿瘤发生风险约为非 MASLD 人群的 2 倍；发病率最高的是肝细胞癌，其次是子宫内膜癌、胃癌、胰腺癌和结直肠癌；此外还发现，MASLD 患者比单纯肥胖人群的恶性肿瘤风险更高，提示 MASLD 可能是导致肥胖人群恶性肿瘤风险增加的原因。一项纳入 26 项研究的 Meta 分析结果显示，MASLD 显著增加结直肠癌、胆管癌、乳腺癌、胃癌、胰腺癌、前列腺癌和食管癌的发生风险[56]。

MASLD 导致恶性肿瘤的机制可能与胰岛素抵抗有关，胰岛素抵抗能诱发抗凋亡效应和脂肪组织功能障碍，进而导致炎症反应和肿瘤增殖[60]。也有研究表明，肠道菌群失调也可能是促进肿瘤发生的因素[61]。

## 六、小结

MASLD 是一种可累及多个系统的全身性代谢性疾病，除肝脏外，还会对心血管系统、肾脏、糖代谢等多个肝外系统产生一定影响。所以对 MASLD 患者进行多学科筛查和管理显得尤为重要。对于肥胖/超重、2 型糖尿病及代谢综合征的患者应常规进行 MASLD 的筛查。对于 MASLD 患者应重视筛查心血管疾病及心血管风险、肾功能不全、糖尿病、肝外恶性肿瘤等肝外并发症。肝外并发症的发生发展与 MASLD 的疾病进展呈明显相关性，及早发现和诊断肝外并发症也有助于判断疾病的严重程度，有助于尽早干预、延缓 MASLD 进展。

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