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非酒精性脂肪肝患者心血管风险的研究现状

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摘　要

非酒精性脂肪肝(Non-Alcoholic Fatty Liver Disease, NAFLD)是慢性肝病的主要原因，被认为是代谢综合征的肝脏表现。NAFLD与胰岛素抵抗、肥胖、血脂异常、糖尿病等因素密切相关，这些因素也是心血管疾病的危险因素。研究数据表明心血管疾病是目前NAFLD患者死亡的主要原因，所以有大量的研究探讨NAFLD与心血管疾病之间的联系，其中有很多研究指出NAFLD可能是促进动脉粥样硬化和冠心病发生发展的独立危险因素。因此，进一步了解NAFLD与心血管疾病之间的关系，以及这种关系的发生机制是非常重要的，这将有利于在一定程度上减少心血管疾病的发病率和病死率。

关键词

非酒精性脂肪肝，心血管疾病，冠状动脉粥样硬化性心脏病，机制，危险因素

Current Status of Research on Cardiovascular Risk in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a major cause of chronic liver disease and is consi-

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dered to be the hepatic manifestation of the metabolic syndrome. NAFLD is strongly associated with insulin resistance, obesity, dyslipidemia and diabetes, which are also risk factors for cardiovascular disease. Research data suggest that cardiovascular disease is currently the leading cause of death in patients with NAFLD, so there are a large number of studies exploring the link between NAFLD and cardiovascular disease, with many of them pointing to the possibility that NAFLD may be an independent risk factor that promotes the development of atherosclerosis and coronary atherosclerotic heart disease. Therefore, it is important to further understand the relationship between NAFLD and cardiovascular disease, as well as the mechanisms by which this relationship occurs, which will help to reduce the incidence of cardiovascular disease and morbidity and mortality to a certain extent.

Keywords

Non-Alcoholic Fatty Liver Disease, Cardiovascular Disease, Coronary Atherosclerotic Heart Disease, Mechanisms, Risk Factors

1. 引言

非酒精性脂肪肝是指除饮酒及其他已知的肝损伤因素外，以肝细胞内脂肪过度积聚为主要特征的一种复杂性的肝脏病变。NAFLD 的诊断需要满足以下标准：1) 通过影像学或组织学检查得到肝脏脂肪变性的证据(虽然肝活检是诊断 NAFLD 的金标准方法，但计算机断层摄影、超声、磁共振等非侵入性成像方法可以更安全、更便宜地使用，且具有良好的敏感性和特异性)；2) 排除导致肝脏脂肪堆积的继发性因素，如大量饮酒、长期使用致脂药物、或某些遗传性疾病等[1]。目前 NAFLD 是全世界慢性肝病的主要病因，一项对 1990 年至 2019 年发表的相关研究的荟萃分析表明 NAFLD 的全球患病率约为 30%，并呈上升趋势[2]，这使其成为了影响人类健康的重要公共卫生问题。NAFLD 被认为是代谢综合征的肝脏表现，其与肥胖、糖尿病或血脂异常等代谢合并症有关[3]，在 Guo 等人的研究中，超重人群的 NAFLD 患病率为 69.99%，肥胖人群的 NAFLD 患病率为 75.27% [4]；在 Zobair 等人的研究中，2 型糖尿病(diabetes mellitus type 2, T2DM)患者中 NAFLD 的全球患病率为 55.5% [5]；而这些因素也与心血管疾病密切相关。现如今心血管疾病位于全球人群死亡原因的首位，其死亡患者总数占全球死亡患者总数的 32%。在我国，心血管疾病的发病率和患病率仍呈明显上升趋势。据数据分析，目前我国心血管疾病现患人数为 2.9 亿，其中冠心病患者占 1100 万；据估计，至 2030 年冠心病的患病人数可达 2263 万[6]。所以对冠心病发生、发展的及早预防和早期干预是十分重要的。近年来关于 NAFLD 与冠心病之间相关性及可能机制的研究越来越多，其中有不少研究指出 NAFLD 可能是促进动脉粥样硬化和冠心病发生发展的独立危险因素[7]，通过对 NAFLD 进行预防和早期诊治可能可以降低冠心病的发病率，延缓冠心病的进展以及改善冠心病的预后。本综述主要讨论 NAFLD 与冠心病的共同危险因素，NAFLD 与冠心病的相关性，相关性背后的可能机制。

2. 非酒精性脂肪肝与冠心病的共同危险因素

众所周知，冠心病传统的主要危险因素有糖尿病、血脂异常、肥胖和不良的生活习惯等[8]。NAFLD 的发生发展也同这些危险因素有着密不可分的联系。2 型糖尿病和糖耐量受损是 NAFLD 发生发展的重要

危险因素[9]。2 型糖尿病与胰岛素抵抗、高血糖、高甘油三酯血症、从脂肪组织到肝脏的游离脂肪酸增加、内脏脂肪堆积有关；而所有这些都与 NAFLD 的风险增加有关。高甘油三酯血症会导致动脉粥样硬化，增加冠心病的风险，在 Zhang 等人的研究中，93.2%的心血管疾病患者的低密度脂蛋白胆固醇水平存在异常[10]。同时高甘油三酯血症也与胰岛素抵抗、糖耐量受损、2 型糖尿病、肝脏脂肪堆积、人体肥胖和代谢综合征相关，从而导致 NAFLD 的风险增加。肥胖是指体内脂肪组织过多，会导致肝脏、心脏等异位脂肪沉积，从而增加 NAFLD 和冠心病发生发展的风险。不良的生活习惯，如不健康的饮食、缺乏运动、吸烟等，都是 NAFLD 和冠心病的危险因素。这些习惯会导致体重增加、血脂异常、血压升高等，增加 NAFLD 和冠心病发生发展的风险。尽管 NAFLD 和冠心病有些共同的危险因素，但并非所有 NAFLD 患者都伴随冠心病，还存在其他可能导致冠心病的独立危险因素。因此，个体差异和其他因素的作用也需要考虑。

3. 非酒精性脂肪肝与冠心病的相关性研究

目前国内外都有大量的研究在探讨 NAFLD 与冠心病的相关性。在 Chia 的研究中，共纳入了 817 名 NAFLD 的患者，结果显示 NAFLD 的严重程度与亚临床冠状动脉粥样硬化之间有着显著的线性趋势，且重度 NAFLD 是亚临床冠状动脉粥样硬化的独立风险因素[11]。在 Pu 的研究中，分析比较 NAFLD 患者的组织学严重程度与其 10 年动脉硬化性心血管疾病(Atherosclerotic Cardiovascular Disease, ASCVD)风险的关系，在纳入的 398 名韩国受试者(平均年龄 57.9 岁；男性，44.2%)，与 ASCVD 风险 < 10%的受试者相比，ASCVD 风险 ≥ 10%的受试者存在更严重的非酒精性脂肪肝炎(Non-Alcoholic Steatohepatitis, NASH)和晚期纤维化($P < 0.05$)，且 NASH (OR = 4.07; 95%CI: 1.40~11.88)或晚期纤维化(OR = 8.11; 95%CI: 1.83~35.98)与 ASCVD 高风险独立相关[11]。在 McNally 等人的研究中，在纳入的 5288 例肝脂肪变性患者，Fib-4 ≥ 2.67 是 NAFLD 组中冠心病的独立危险因素。在 Fib-4 值低于 2.67 时，作为连续变量的 Fib-4 与 NAFLD 患者的冠心病风险呈线性相关[12]。在一项纳入了 5,802,226 名患者的荟萃分析中，经过中位 6.5 年的随访，共有 99,668 名患者出现 ASCVD。结果显示，NAFLD 可明显增加 ASCVD 的风险(HR = 1.45; 95%CI 1.31~1.61)，且随着 NAFLD 严重程度的增加，ASCVD 的风险同步增加，尤其是在肝硬化阶段(HR = 2.50; 95%CI 1.68~3.72) [13]。在一项国内的研究中，共纳入 1683 名无症状的患者(平均年龄，63.3 ± 9.4 岁；1117 名男性)，在随访中，NAFLD 组比非 NAFLD 组显示出更高的冠脉斑块进展率(33.0% vs 16.6%, $P < 0.001$) [14]。因此目前大量研究均表明 NAFLD 与心血管事件尤其是冠心病的发生与发展密切相关。

4. 非酒精性脂肪肝与冠心病相关性的可能机制

4.1. 低级别全身性炎症

NAFLD 通过肝脏和脂肪组织之间复杂的相互作用引起全身炎症反应[15] [16]。游离脂肪酸会诱导肝细胞分泌肿瘤坏死因子(TNF-α)、白细胞介素-6 (IL-6)和白细胞介素-8 (IL-8)，从而诱导全身炎症反应[17] [18]。一项有 2482 名参与者的研究发现，在调整了体重指数和代谢综合征的其他成分后，脂肪肝的发生发展与血清全身炎症标志物的浓度升高独立相关，这些标志物包括 c 反应蛋白、尿异前列腺素、IL-6、细胞间粘附分子 1 等[19]。全身炎症反应与心血管疾病的发生发展也有关[20]。NAFLD 继发的低级别全身炎症反应可导致促炎细胞因子释放，并可能通过诱导内皮功能障碍和促进斑块形成而促进动脉粥样硬化性心血管疾病的发展[21] [22] [23]。

4.2. 心外膜脂肪组织

NAFLD 与心外膜脂肪组织增加有关，且心外膜脂肪厚度的高低与肝纤维化的严重程度有关[24] [25]。

心外膜脂肪组织与冠状动脉和心肌紧密相连，与心肌共享一个微循环，并分泌促炎细胞因子，如 IL-6 和 TNF-α，通过诱导内膜浸润和纤维化促进动脉粥样硬化和心力衰竭[26] [27]。一项对 147 例活检证实的 NAFLD 患者的研究发现，心外膜脂肪堆积和心脏功能改变在重度肝纤维化患者中更为明显[25]。这些数据表明 NASH 和心血管疾病可能共享某种与异位脂肪组织堆积及全身炎症反应相关的机制，但目前仍需要更多的研究来验证这一假设。

4.3. 胰岛素抵抗

糖代谢异常和胰岛素抵抗是 NAFLD 和心血管疾病的关键驱动因素。骨骼肌胰岛素抵抗将葡萄糖从骨骼肌糖原合成转移到肝脏[28]。转移到肝脏的葡萄糖增多，会伴随着高胰岛素血症，这将刺激固醇调节元件结合蛋白 1c (SREBP1c)，促进调节脂肪生成的关键肝酶的表达增加，导致极低密度脂蛋白的产生增加，从而导致高甘油三酯血症和 NAFLD [15] [29]。高甘油三酯血症、高胰岛素血症进一步触发肝脏糖异生，进一步增加胰岛素水平，从而促进糖代谢异常的恶性循环。胰岛素抵抗是动脉粥样硬化性心血管疾病一个强有力的预测因子[30] [31]，高水平胰岛素通过多种机制加速动脉粥样硬化的过程[32]。这些均可表明胰岛素抵抗在 NAFLD 和心血管疾病发病机制中的关键性。

4.4. 内皮功能障碍

内皮功能障碍是动脉粥样硬化发生的起点[33]。不对称二甲基精氨酸(ADMA)升高的常源自肝脏功能的损害，并且通常可以在 NAFLD 患者中检测到[34]。ADMA 水平升高导致保护性血管舒张分子-NO 可用性降低，这可能导致血管舒缩调节或血管通透性紊乱以及血小板功能障碍[34] [35]。在 Tomas 等人的研究中，在 886 名患者中发现，NAFLD 组与非 NAFLD 组的患者相比，血管内皮功能障碍的发生率更高(64.8% vs 43.4%; $P < 0.001$)且冠脉血流储备更低(1.9 ± 1.1 vs 2.2 ± 0.7; $P < 0.001$) [36]。此外，NAFLD 患者的同型半胱氨酸水平较高，这可进一步诱导氧化应激和内皮功能障碍从而促进动脉粥样硬化的发生[37] [38] [39]。由此可见，内皮功能障碍可能在 NAFLD 患者心血管疾病的发生发展中起到重要作用。

4.5. 肠道微生物失调与全身炎症

NAFLD 与肠上皮细胞间紧密连接的破坏有关，导致肠道通透性增加，肠道细菌和脂多糖的易位[40]。一项前瞻性研究采用全基因组测序技术，从活检证实的 NAFLD 患者的粪便中提取脱氧核苷酸，发现晚期肝纤维化与促炎革兰氏阴性变形杆菌(包括大肠杆菌)数量增加有关[41]。一项对动脉粥样硬化性心血管疾病患者与健康对照组进行的宏基因组相关性研究发现，革兰氏阴性细菌(包括大肠杆菌)数量在动脉粥样硬化性心血管疾病患者中增加[42]。这些研究表明，NAFLD 患者的肠道微生物失调可导致全身炎症，并可能加剧心血管疾病[21] [43] [44] [45]。

5. 小结

综上所述，NAFLD 与冠心病之间具有较强的相关性。NAFLD 的胰岛素抵抗、心外膜脂肪组织堆积、炎症和内皮功能障碍、肠道微生物失调可能是冠心病发生发展的重要机制。通过对 NAFLD 的早期干预及治疗，可降低心血管疾病的发生率、延缓心血管疾病的进展及改善心血管疾病的预后。大量研究表明 NAFLD 患者发生冠心病的风险增加，但 NAFLD 是否是冠心病的独立危险因素目前尚未明确，对此后续仍需大量研究。

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