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文献综述 REVIEW

非酒精性脂肪性肝病在心血管疾病发生发展中的作用

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Role of non-alcoholic fatty liver disease in development of cardiovascular disease

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Abstract

With the improvement of the economic level and changes in dietary structure and lifestyle, the incidence of non-alcoholic fatty liver disease (NAFLD) has been increasing. It has gradually become the main cause of chronic liver diseases in the world. Cardiovascular disease (CVD) is the main cause of death in NAFLD patients, and more and more studies have found that there is a correlation between the two conditions. NAFLD patients are at greater risk of developing CVD than normal patients. Associated mechanisms may be related to dysfunction of blood vessels and endothelial cells, bile acid metabolism, oxidative stress, systemic inflammation, and activation of the renin-angiotensin system. Among them, metabolic syndrome plays an important role. Therefore, early identification of cardiovascular disease-related risk factors in NAFLD patients and thereby reducing cardiovascular-related complications are essential to improve the prognosis of those patients.

Key Words: Non-alcoholic fatty liver disease; Cardiovascular disease; risk factors; Epidemiology; metabolic syndrome

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摘要

随着经济水平的提高、饮食结构和生活方式的改变, 非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)的发病率不断上升, 逐渐成为全球慢性肝病的主要病因. 心血管疾病(cardiovascular disease, CVD)作为NAFLD患者的主要死亡原因, 越来越多的研究发现两者之间存在相关性; NAFLD患者CVD发生发展的风险更大, 其机制可能与血管和内皮细胞功能障碍、胆汁酸代谢、氧化应激、全身炎症反应和肾素-血管紧张素系统的激活等相关. 其中, 代谢综合征在两者联系中发挥了重要的作用. 因此, 早期识别

NAFLD患者心血管疾病相关危险因素, 进而减少心血管相关并发症, 对于改善该类患者的预后至关重要.

关键词: 非酒精性脂肪性肝病; 心血管疾病; 危险因素; 流行病学; 代谢综合征

核心提要: 越来越多的研究证实心血管疾病与非酒精性脂肪性肝病之间存在相关性, 其机制主要包括代谢综合征和其他病理生理相关, 故早期识别非酒精性脂肪肝病患者心血管疾病相关危险因素对于改善该类患者的预后至关重要.

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0 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是目前最常见的慢性肝病, 近年来其发病率不断攀升, 已成为全球性的健康问题, 在我国NAFLD甚至已取代慢性乙型肝炎成为第一大慢性肝病[1]. 据世界卫生组织统计, 心血管疾病(cardiovascular disease, CVD)是世界范围内死亡的主要原因, 对居民健康及卫生经济都造成了巨大的负担. 同样, CVD也是NAFLD患者死亡的主要原因[2]. 在过去几年的研究中发现, NAFLD与CVD密切相关[3]. 因此, 对于NAFLD患者来说, 尽早识别CVD相关的危险因素, 对于改善患者预后具有重大意义. 本文就NAFLD与CVD之间的联系作一综述, 重点探讨NAFLD对CVD发生的影响及潜在的机制.

1 NAFLD和CVD的流行病学

NAFLD是指除外酒精和其他对肝脏有明确损害因素所引起的, 以脂肪在肝细胞内过度沉积为主要病变特征的临床病理综合征. 它的疾病谱包括单纯性脂肪肝、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)、肝纤维化、肝硬化以及肝细胞癌[1]. 目前, 全球范围内NAFLD的患病率为25.24%, 在肥胖人群或2型糖尿病患者中, NAFLD的患病率高达70%-90%[4]. CVD是全世界最常见的死亡原因, 占全球死亡人数的31%. 2019年, 据估计有1860万人死于CVD[5]. Wu等人[6]通过对34项研究进行荟萃分析, 通过排除共同的危险因素, 如吸烟和2型糖尿病等, 结果发现NAFLD与CVD的发生风险增加相关, 尤其是冠心病和高血压. 另有研究也表明[7-9], NAFLD与CVD的不同表型之间也存在着密切的关系, 例如动脉粥样硬化性心脏病、心肌病、瓣膜病以及心律失常等. 由此可见, NAFLD是CVD发生发展的独立危险因素.

2 代谢综合征在NAFLD影响CVD发生发展中的作用

代谢综合征(metabolic syndrome, MetS), 即腹型肥胖、胰岛素抵抗、血糖和血压升高、血脂异常和低度全身炎症状态[10], 是一组复杂的代谢紊乱症候群. NAFLD中的肝脂肪堆积是MetS在肝脏的表现, 美国第三次国家健康与营养检查调查证实, MetS患者发生NAFLD的风险极高(OR: 11.5, 95%CI: 8.9-14.7)[11]. 而MetS与CVD同样密切相关, Mottillo等[12]对87项研究进行荟萃分析, 结果发现MetS患者CVD的发生风险显著增加(RR: 2.35, 95% CI: 2.02-2.73), CVD相关的死亡率增加1倍以上(RR: 2.40, 95%CI: 1.87-3.08). 在NAFLD中, 血脂谱会发生显著改变, 主要体现在甘油三酯(triglyceride, TG)和低密度脂蛋白(low density lipoprotein, LDL)水平升高, 高密度脂蛋白(high density lipoprotein, HDL)降低, 从而导致TG/HDL、总胆固醇(total cholesterol, TC)/HDL以及LDL/HDL比率异常, 而这些都被认为是动脉粥样硬化的危险因素[13]. 另外, 肝脏脂肪含量可以反映心肌内脂肪的积聚情况, 心肌脂肪变性会引起心肌细胞的代谢和功能障碍[14]. 研究表明NAFLD与心外膜脂肪组织(epicardial adipose tissue, EAT)的出现独立相关, 而EAT不仅与冠状动脉钙化相关[15], 同时也能通过分泌促炎因子, 例如白介素(interleukin, IL)-1、IL-6和肿瘤坏死因子(tumor necrosis factor, TNF), 从而在房颤和心血管自主神经功能障碍中发挥作用[16]. 另有研究表明[17], 肝脂肪堆积的严重程度与前蛋白转化酶枯草杆菌蛋白酶9(proprotein convertase subtilisin kexin type 9, PCSK9)的水平有关, PCSK9是一种肝源性肽, 通过抑制肝细胞摄取LDL从而导致心血管风险的增加. 在MetS组分胰岛素抵抗方面, 肝脏胰岛素信号传导被抑制, 造成肝脏脂质积聚并产生脂毒性; 而胰岛素抵抗的患者中, 肝脏会增加甘油三脂的分泌, 从而使得循环中甘油三酯的水平升高, 增加心血管疾病的风险[18]. 另外, 一些肝脏特异性细胞因子可以影响胰岛素敏感性, NAFLD患者血清胎球蛋白-A水平升高, 并被证实与发生心肌梗死的高风险相关[19]. 因此, MetS各大组分都不仅是NAFLD和CVD共同的危险因素, 同时NAFLD可以通过MetS进一步参与CVD的发生发展.

3 NAFLD影响CVD发生发展的其他机制

除MetS外, 近年来, 越来越多的研究表明, NAFLD患者的促炎症、促动脉粥样硬化和促血栓形成的内环境对于

CVD发生发展也至关重要[20]. NAFLD患者这种内环境形成与遗传因素, 包括葡萄糖激酶调节蛋白(glucokinase regulatory protein, *GCKR*)基因、含patatin样磷脂酶域3(patatin-like phospholipase domain-containing 3, *PNPLA3*)基因, 以及跨膜6超家族成员2(transmembrane 6 superfamily member 2, *TM6SF2*)等基因, 的影响密切相关[21].

在血管和内皮细胞功能方面, NAFLD通过血管和内皮功能的改变影响CVD发生发展. NAFLD与肝脏微血管的改变相关, 且存在系统性内皮功能障碍, 这也是动脉粥样硬化的早期表现[22]. 非对称性二甲基精氨酸(asymmetric dimethylarginine, ADMA)是一氧化氮合酶的内源性拮抗剂, 由于其分解主要依赖于肝脏, 所以NAFLD患者中ADMA的水平升高, 从而引起血管的舒张功能改变[22]. 除此以外, NAFLD的发展中伴随着血管重构的发生, 其中血管内皮生长因子(vascular endothelial growth factor, VEGF)扮演了重要的角色, 而VEGF家族成员, 尤其是VEGF-A是公认的致动脉粥样硬化因子, 在斑块不稳定性中发挥了重要的作用[23]. 所以, NAFLD患者中血管和内皮功能的改变, 在CVD的发生发展过程中发挥重要作用.

其次在胆汁酸代谢方面, NAFLD患者胆汁酸稳态被破坏, 损害糖脂代谢稳态、加重胰岛素抵抗, 且血清胆汁酸水平随着疾病进展而升高[24]. 而胆汁酸被证实存在心脏毒性, 可损害心室功能, 并与房颤发生的风险增加有关[25]. 此外, 调控胆固醇和胆汁酸稳态的法尼醇X受体(farnesoid X receptor, FXR)曾被证实在动脉粥样硬化中发挥作用, 最新的研究表明抑制肠道FXR/鞘磷脂磷酸二酯酶3(sphingomyelin phosphodiesterase 3, SMPD3)轴可以缓解动脉粥样硬化, 表明NAFLD患者应该尽早监测胆汁酸水平, 并且可以通过进一步的研究在NAFLD患者中干预胆汁酸代谢预防或治疗CVD的可行性[26].

另外在氧化应激及系统炎症方面, NAFLD状态下肝脏释放的炎性细胞因子可能导致全身炎症和CVD的发生, 例如IL-6、C-反应蛋白和肿瘤坏死因子-α等, 这些炎症因子通过引起内皮功能、血管张力和凝血系统的改变, 进而促进斑块的形成, 从而触发CVD[27].

4 结语

综上所述, NAFLD在CVD发生发展中发挥了重要作用, 不仅在于两者之间有着共同危险因素-MetS, NAFLD还带来了CVD发生发展的额外风险, 包括血管和内皮细胞功能障碍、胆汁酸代谢、氧化应激和全身炎症反应等. 而MetS作为连接两者的桥梁, 揭示了代谢因素在NAFLD和CVD发生发展的重要作用. 近年来, NAFLD定义中的“非酒精性”使得临床医生和患者缺乏对“代谢”因素的关注, 而这在NAFLD的发生及并发症的管理方面至关重要. 因此, 在2020年, 国际专家组共识声明提出, 将NAFLD重命名为“代谢功能障碍相关性脂肪性肝病(metabolic dysfunction associated fatty liver disease, MAFLD)”[28]. 这样的更名不仅强调了其发病机制, 还让临床医生与患者更多的关注到代谢障碍相关的其他疾病, 例如血脂异常、2型糖尿病、冠状动脉粥样硬化性心脏病等. 基于MAFLD和CVD的密切关系, 以及代谢因素对于两者的重要作用, NAFLD患者应该早期监测心血管系统的代谢、结构和功能改变, 这有助于完善NAFLD患者心血管风险评估, 减少NAFLD患者CVD以及相关并发症的发生, 最终有助于改善NAFLD患者的预后.

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