Advances in Clinical Medicine 临床医学进展, 2019, 9(9), 1073-1079
Published Online September 2019 in Hans. http://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2019.99165

Hans汉斯

Progress in the Study of the Pathogenesis of Chronic Kidney Disease Associated with Nonalcoholic Fatty Liver Disease

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Received: Aug. 15th, 2019; accepted: Aug. 29th, 2019; published: Sep. 10th, 2019

Abstract

With the increase of obesity and Type 2 Diabetes Mellitus (T2DM), non-alcoholic Fatty Liver Disease (NAFLD) has become the most common chronic Liver Disease in the world. NAFLD is a multi-system disease closely associated with metabolic syndrome, cardiovascular disease and chronic kidney disease. In recent years, the prevalence of chronic kidney disease (CKD) increases year by year, which has become a global public health problem and a serious threat to human health. Many studies have shown that NAFLD is associated with impaired renal function. The early manifestations of kidney injury are podocyte injury and proteinuria. Therefore, NAFLD and CKD have gradually become the focus of attention of scholars. We speculate that there is a common pathogenesis between NAFLD and CKD. The purpose of this article is to summarize the pathogenesis of CKD associated with NAFLD.

Keywords

Non-Alcoholic Fatty Liver Disease, Chronic Kidney Disease, Podocyte Injury, Proteinuria

非酒精性脂肪肝相关慢性肾病发病机制进展

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收稿日期：2019年8月15日；录用日期：2019年8月29日；发布日期：2019年9月10日

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文章引用: 宋清莲, 袁贝贝, 刘京京, 刘万里, 戴光荣. 非酒精性脂肪肝相关慢性肾病发病机制进展[J]. 临床医学进展, 2019, 9(9): 1073-1079. DOI: 10.12677/acm.2019.99165

摘　要

随着肥胖和2型糖尿病(Type 2 Diabetes Mellitus, T2DM)发病率的上升，非酒精性脂肪肝(Non-alcoholic Fatty Liver Disease, NAFLD)已经成为全球最常见的慢性肝病。NAFLD是一种多系统疾病，与代谢综合征、心血管疾病，慢性肾脏病密切关联。近年来，慢性肾脏病(Chronic Kidney Disease, CKD)患病率逐年上升，已成为全球性的公共卫生问题，严重威胁人体健康。很多研究表明，NAFLD与肾功能受损相关。肾脏损伤的早期表现为足细胞损伤和蛋白尿。因此，NAFLD与CKD逐渐成为学者们关注的热点。我们推测NAFLD与CKD之间存在共同发病机制。本文目的在于对非酒精性脂肪肝推测相关慢性肾病发病机制进行综述。

关键词

非酒精性脂肪肝，慢性肾病，足细胞损伤，蛋白尿

1. 引言

随着肥胖和 T2DM 发病率的增加，普通成人非酒精性脂肪肝(Non-Alcoholic Fatty Liver Disease, NAFLD)患病率为6.3%~45%，其中10%~30%为非酒精性脂肪性肝炎(Non-Alcoholic Steatohpatitis, NASH)，已经成为世界上最常见的慢性肝病[1]。疾病谱包括非酒精性单纯性脂肪肝(Non-Alcoholic Simple Fatty Liver Disease, NAFL)，其从NASH逐渐发展为非酒精性脂肪性肝硬化，最后发展为肝细胞癌(Hepatocellular Carcinoma, HCC)。NASH 是 NAFLD 患者发生肝硬化和 HCC 的必要阶段，也是最关键的环节。近年来，CKD 患病率逐年增加，已成为世界公共卫生问题。许多研究表明[2] [3] [4] [5] [6]，NAFLD 与肾功能受损密切相关，与 CKD 独立相关。CKD 是心血管疾病、糖尿病以及恶性肿瘤之后对人类健康的另一个严重威胁。它给社会带来的经济负担是毋庸置疑的，因此必须及早发现 CKD 及其潜在风险因素。本文目的在于对非酒精性脂肪性肝病推测相关慢性肾病发病机制进行综述。

NAFLD 与 CKD 有着共同的发病机制，NAFLD 相关 CKD 的发病机制可归纳如下：

2. 胰岛素抵抗(Insulin Resistance, IR)

作用机制在 NAFLD 的发病机制中“首次打击学说”认为 IR 是主要发病因素之一[7]。高血糖可以促进新生脂肪的生成，胰岛素通过激活转录因子甾醇调节元件结合蛋白 1c (SREBP-1c)调控新生脂肪生成[8]。同时，脂质中间代谢产物二酰甘油(DAG)能激活蛋白激酶 C，影响胰岛素信号传导通路[9]。另有研究表明[10]，IR 能促进肝纤维化。因此，IR 与 NAFLD 密切相关。

IR 与许多疾病如心血管疾病(Cardiovascular disease, CVD)、CKD、T2DM 相关联。IR 会导致肾脏结构及功能障碍[11]。胰岛素对肾小管有保钠作用。在高胰岛素血症的情况下，肾脏对血压的盐敏感性是它的直接作用增强，使肾小球囊内压升高，渐而出现微量蛋白尿[12]，也可通过间接作用包括激活肾素－血管紧张素－醛固酮系统、交感神经系统促进肾脏损害[13]。肾脏足细胞是胰岛素的敏感细胞[14]。足细胞是一种附着在肾小球基底膜外侧的上皮细胞，也是构成肾小球滤过屏障的重要结构，通过阻止蛋白质滤

过维持肾脏正常功能。因此，足细胞损伤是出现蛋白尿的关键因素。足细胞主要通过胰岛素信号传导通路维持肾脏功能。研究表明[15]，足细胞 IR 在糖尿病肾病早期就已经存在。Welsh 等研究发现[16]，敲除小鼠足细胞胰岛素特异性受体可引起蛋白尿和肾小球硬化。当脂质代谢紊乱、炎症反应等损伤足细胞时，通过影响胰岛素信号传导通路导致 IR。

3. 高脂血症

作用机制：NAFLD 的特征在于脂肪在肝细胞中以含有甘油三酯的脂滴形式积累。目前认为[17]肝脏甘油三酯主要来源于三个方面包括 IR 的脂肪组织中游离脂肪酸释放增加，肝内新生脂肪增加以及过度高脂肪食物的摄入。以甘油三酯这种形式积聚被认为是发挥脂毒性之前对机体的一种保护方式。NASH 的进展是脂质介导的脂毒性和炎症相互作用介导而导致肝损伤[18]。肝脏有害脂类物质增多(如 DAG、棕榈酸酯、神经酰胺等)使 NAFLD 向 NASH 转化导致肝细胞损伤，坏死，炎症细胞通路激活(如内质网应激，氧化应激等)，从而使级联反应放大，促进疾病发展[19]。

过多的脂肪贮积也会使脂肪沉积在异位脏器。脂毒性是指脂质在非脂肪组织的异位沉积，过量的游离脂肪酸通过促进内质网应激和活性氧的过量产生导致组织器官功能障碍。脂代谢紊乱会导致肾小球损伤以及肾脏疾病进行性发展[20] [21]。越来越多的证据表明[2] [5] [22]，甘油三酯与 CKD 密切相关。其具体机制尚不清楚。血液中甘油三酯通过与载脂蛋白结合而转运至肝外组织。高甘油三酯血症与足细胞损伤有关[23]。极低密度脂蛋白是运输内源性甘油三酯的主要形式，血浆中高游离脂肪酸和甘油三酯促进肾小球细胞对含有甘油三酯的极低密度脂蛋白摄取和结合。反过来，肾小球甘油三酯积聚增加，导致动脉粥样硬化和足细胞损伤，而足细胞中游离脂肪酸沉积可过多导致足细胞凋亡[24] [25]。肾脏系膜细胞是一种肾脏固有细胞，具有分泌细胞基质、产生细胞因子、吞噬和清除大分子物质等生物学作用。高脂血症中的低密度脂蛋白和极低密度脂蛋白氧化产生的 OX-LDL 有细胞毒性作用[26]，一方面可能会增加自由基和细胞因子的释放损害肾脏；另一方面可能会刺激系膜细胞增生，损伤肾脏内皮细胞，增大细胞通透性，增加细胞基质的分泌，渐而出现肾小球硬化，最终成为 CKD 发生发展基础。

4. 脂联素(Adiponectin, APN)

作用机制 APN 是由脂肪细胞分泌的一种细胞因子，并广泛分布于人体组织。APN 主要参与糖脂代谢、胰岛素抵抗、氧化应激、炎症反应发挥抗炎、抗纤维化、抗氧化、调节血脂、血糖、增加胰岛素敏感性等作用等[27]。APN 主要通过与受体结合发挥生物学作用。APN 与受体结合后，通过激活丝裂原活化蛋白激酶(MAPK)通路和磷脂酰肌醇 3 激酶-蛋白激酶 B(IP3-AKT/PKB)通路上调胰岛素及其受体的表达和减轻炎症反应水平，从而改善 IR [28]；APN 还可以通过降低脂质代谢产物神经酰胺水平改善 NAFLD 小鼠模型 IR [29]。研究表明[30]，NASH 患者血浆 APN 水平降低程度与肝组织损伤严重程度有关。证明 APN 在 NAFLD 发生发展中起着重要作用。ANP 主要通过影响肝星状细胞(HSC)活化和 IR，促进肝纤维化[31] [32]。ANP 对 HSC 的影响表现为，通过调控水通道蛋白抑制 HSC 活化促进肝纤维化[33]。

APN 与肾脏足细胞密切相关。Sharma 等[34]对小鼠敲除脂联素的研究发现，该组小鼠蛋白尿水平较对照组升高。Ramacharaoandr 等[35]也得出同样的结论，此外他们研究组还发现敲除脂联素的小鼠，足细胞足突消失，当外源性给予脂联素可减轻蛋白尿，改善足细胞形态和肾小球 AMPK 活性增强。说明 APN 可以通过激活 AMPK 通路，维持足细胞的正常结构与功能。该研究对 20 名肥胖受试者血浆 APN 浓度与尿白蛋白排泄率进行相关性分析，得出 P 值为 0.002，说明 ANP 与尿蛋白呈负相关，与既往研究结果一致[36]，表明 ANP 对肾脏有保护作用。最近研究表明[37] [38]，ANP 与 CVD 密切相关，血浆低水平的 APN 可作为抗动脉粥样硬化。

5. 氧化应激和炎症介质

作用机制 NAFLD 的发病机制“二次打击学说”认为氧化应激和炎症介质是 NAFLD 疾病进展的关键[39] [40]。近年来研究发现，氧化应激在 NAFLD 早期就参与[41] [42]。促炎细胞因子包括 IL-6，TNF-α，IL-4 等在 NAFLD 发病机制中发挥重要作用[43]。丝裂原活化蛋白激酶(MAPK)是肝脏中氧化应激的重要调节蛋白。MAPK 通路和核转录因子 NF-κB 通路是肝细胞氧化应激损伤的两个重要途径[44]。通路调控机制较复杂，主要通过激活下游转录因子来调控肝细胞损伤、死亡。在生理条件下，人体仅产生少量活性氧(ROS)来维持正常生理功能而不会对机体造成损害。当 NAFLD 发生时血浆游离脂肪酸和脂肪酸 β 氧化增加，使 ROS 产生增多比体内抗氧化酶系统(谷胱甘肽、超氧化物歧化酶、过氧化氢酶等)增加更多，触发 MAPK 活化并启动细胞传导通路。在该途径中，发生氧化应激导致肝细胞受损甚至坏死，并且坏死细胞引起炎症细胞侵入肝实质导致 NASH [45]。可见，氧化应激是 NASH 的主要驱动力之一。ROS 通过与细胞内脂质反应出现脂质过氧化。活性氧自由基 8-羟基脱氧鸟苷作为氧化应激线粒体 DNA 损伤生物学标志物。已有研究表明[46]，NASH 患者肝细胞过表达 8-羟基脱氧鸟苷和抗氧化物消耗增加。而关于 NASH 是否是一种抗抗氧化酶缺乏状态，有待进一步研究明确。

ROS 不仅参与 NASH 的发生发展，此外，它在 CKD 发生发展具有重要作用[47]。氧化应激可增加脂质过氧化和炎症因子的释放，从而导致足细胞的结构与功能障碍。足细胞过量的游离脂肪酸与 IR、ERS 密切相关[14] [48]。氧化应激和炎症反应是脂毒性的重要结果。慢性炎症是促进足细胞损伤和肾小球硬化的重要机制[49]。炎症介质还可能介导系膜细胞氧自由基产生，进一步使脂蛋白氧化，炎症本身可直接氧化脂蛋白，并能消除防止脂蛋白氧化的潜在的防御机制，从而使脂质肾损害的程度进一步加重。

6. 内质网应激(Endoplasmic Reticulum Stress, ERS)

作用机制脂质超载引起 ERS 是一种重建内质网稳态模式。它的长期激活会触发炎症细胞通路和发生脂毒性。GRP78 作为分子伴侣在调控 ERS 信号传导通络中发挥重要作用。ERS 通过释放 GRP78 来激活下游介质如 PERK、IRE-1 等。GRP78-IRE1-JNK 通路激活介导肝细胞死亡[50]。ERS 还可以通过诱导自噬加重脂肪性肝炎[51]。研究表明[52]，NAFLD 患者体内过多饱和脂肪酸摄入，会引起 ERS 和炎症反应。

在糖尿病肾病中，游离脂肪酸、高血糖、胰岛素信号传导通路障碍可以激活足细胞发生 ERS [53] [54]。肾 ERS 也是蛋白尿的发病因素之一[55]。棕榈酸是血浆丰富的游离脂肪酸。研究发现[56]，棕榈酸可以诱导足细胞应激和细胞死亡。而胰岛素受体过表达可保护足细胞免于 ERS 和细胞凋亡[57]。虽然研究发现抑制 ERS 可以减少蛋白尿和肾纤维化，但仍需更多的研究来证实。体外实验证实[58]，肾小管上皮细胞脂质超载能够引起 ERS。所以，ERS 不仅对肾小球有影响，对肾小管也有影响。

7. 总结

NAFLD 是一种多系统疾病，不仅与肝脏相关疾病的发病率和死亡率有关[59]，还与发生肝外重要脏器慢性疾病如 T2MD、CVD、CKD 的发病风险增加相关[60]。因此，早期发现疾病相关危险因素干预和检测对于患者预后至关重要。IR、APN、ERS、高脂血症、氧化应激、炎性因子释放相互作用，共同参与 CKD 与 NAFLD 发生与发展。尽管二者有共同的发病机制，但因果关系仍不确定，有待进一步深入的研究来明确。肾损伤早期虽然表现为蛋白尿，但仍缺乏肾脏组织学活检来证实。所以，今后仍需要大量研究通过组织学活检来进一步明确是否存在肾脏结构器质性损害，从而为临床治疗提供新思路。

基金项目

陕西省社会发展科技攻关项目(2016SF-120)。

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