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NAFLD 与 2 型糖尿病的关系及其研究进展

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[摘 要] 随着肥胖及2型糖尿病(type 2 diabetes mellitus,T2DM)的流行,非酒精性脂肪性肝病(Non—alcoholic fatty liver disease,NAFLD)的发病率日益剧增,严重威胁人类健康。T2DM会加速NAFLD肝病的进展。反之亦然。NAFLD和糖尿病协同作用,形成恶性循环,导致不良临床事件的发生。尽管NAFLD在T2DM患者中的患病率很高,但在临床工作中常常不被引起重视。本篇综述将重点描述这两种代谢之间因果关系的发病机制及治疗,为临床治疗T2DM合并NAFLD提供理论依据。
[关键词] 2型糖尿病；非酒精性脂肪性肝病；发病机制；治疗
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The relationship between non-alcoholic fatty liver disease and type 2 diabetes mellitus and its research progress

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[Abstract] With the prevalence of obesity and type 2 diabetes (T2DM),the incidence of NAFLD(Non—alcoholic fatty liver disease,NAFLD) is increasing dramatically, which is a serious threat to human health. T2DM can accelerate the progression of NAFLD liver disease. And vice versa. NAFLD and diabetes work together to form a vicious cycle that leads to adverse clinical events. Despite the high prevalence of NAFLD in patients with T2DM, it is often overlooked in clinical practice. This review focuses on the pathogenesis and treatment of the causal relationship between these two metabolisms, providing theoretical basis for clinical treatment of T2DM with NAFLD.
[Key words] Type 2 diabetes mellitus; nonalcoholic fatty liver disease; pathogenesis; treatment

随着肥胖、糖尿病和代谢综合征的全球化流行,NAFLD发病率逐年上升,NAFLD已成为全球最严重的肝脏疾病之一,严重危害公众健康。NAFLD是常见的慢性肝脏疾病,其疾病谱包括从孤立性肝脂肪变性到非酒精性脂肪性肝炎(NASH)、晚期纤维化(AF)、肝硬化、肝细胞癌(HCC)的发展[1]。NAFLD在一般人群中的患病率估计为25%[2],T2DM患者的NAFLD患病率高达75%,[3]重度肥胖患者的患病率甚至高达90%。2020年国际专家一致提出了一种新的疾病实体“代谢功能障碍相关脂肪肝病”(MAFLD)[4]。85%的NAFLD患者中至少有1/3患者存在代谢风险因素,建议将NAFLD更名为代谢相关性脂肪性肝病(MAFLD),此概念的提出更加强调了NAFLD、肥胖及T2DM之间的相关性[5]。胰岛素抵抗(IR)是T2DM的重要发病机制,而NAFLD的发生与发展也与IR密切相关,IR可能是两者同时发生的枢纽,本文旨在总结目前关于NAFLD与T2DM关系以及NAFLD发病机制及治疗的文献,重点介绍近期研究。

1 T2DM与NAFLD关系

T2DM是全球最常见的慢性疾病之一,越来越多的证据表明T2DM与NAFLD具有相关性。T2DM患者中NAFLD的患病率是普通人群的两倍多,达到近60%,其中三分之一的患者存在NASH[6]。NAFLD与T2DM之间的双向关系已被充分证实[7,8]。T2DM促进NAFLD进展为肝硬化,会使肝脏相关的疾病死亡的风险增加两到三倍[9,10]。反之,NAFLD的存在也会对T2DM的发病率和相关的不良临床结果产生负面影响。最近的证据表明,T2DM是NAFLD的独立危险因素[11],反之亦然。两者协调作用,相互共存,形成恶性循环。诊断为NAFLD的个体患T2DM的风险增加2倍,发生肿瘤、心血管疾病和肾脏疾病的风险更高,尤其是与T2DM相关时。T2DM合并NAFLD会增加糖尿病慢性并发症发生,包括大血管和微血管并发症[12,13],使其病情加重。同时也使NAFLD向更严重方向发展,NAFLD会进展为NSAH、肝纤维化、甚至肝细胞癌[14]。因此,对T2DM合并NAFLD早期预测和干预可能会降低心血管风险和NAFLD进展速度。

2 NAFLD发病机制

在NAFLD中,其基本的病理生理机制是胰岛素抵抗,肝脏,脂肪组织和肌肉的胰岛素敏感性受损,这也是导致糖尿病过程的决定因素。T2DM促进NAFLD发生、发展,反之亦然,两者协同促进,形成恶性循环。研究表明,NAFLD的发展与IR、功能失调的脂肪组织、炎症反应、内质网应激和肠道菌群失调有关。

2.1胰岛素抵抗

IR是T2DM以及NAFLD发病的关键因素。IR是指机体需要更多胰岛素才能满足正常需要的反应。胰腺可以通过增加胰岛素的产生来满足机体需求,从而导致高胰岛素血症。当高胰岛素水平不再足以维持代谢平衡时,最终会导致胰腺β细胞耗竭、β细胞质量减少、高血糖、糖尿病前期以及糖尿病[4]。IR是肝细胞脂肪堆积的主要原因,胰岛素具有抑制脂肪分解作用,介导脂肪组织中甘油三酯(TG)的储存,并促进脂肪酸的酯化和储存[15]。在IR下,胰岛素抑制脂肪分解的作用会下降,导致游离脂肪酸(freefattyacids,FFA)的大量释放[16]。一方面,大量的FFA以TG的形式储存在肝脏中,导致脂肪堆积并引起NAFLD[17]。另一方面,大量的FFA激活c-JunN末端激酶(JNK),促进肝脏脂肪堆积,导致脂肪生成增加和脂肪酸氧化受损(FAO),引发肝脏炎症和肝纤维化[18]。在NAFLD患者中,肝细胞中的从头脂肪合成(DNL)增加,其与IR密切相关[19]。IR激活脂肪生成转录因子(SREBP-1c),促进肝细胞DNL18。T2DM时,葡萄糖浓度升高可激活ChREBP调节脂肪酸合酶(fattyacid synthase,FAS)的表达,从而促进肝细胞中的DNL,促进NAFLD的发生。

2.2脂肪组织和炎症反应

脂肪组织功能障碍和炎症反应是 NAFLD 发病机制中的关键之一[20,21]。功能失调的脂肪组织会改变脂肪因子的产生,导致促炎脂肪因子增加,抗炎脂肪因子减少[22]。促炎脂肪因子激活c-Jun NH2-末端激酶和核因子κB通路,参与脂肪组织IR和炎症的恶性循环,并促进全身IR和全身炎症的发展。脂肪的快速分解增加了游离脂肪酸的排放,并且在IR的存在下,有利于肝脏从头脂肪生成,为肝脏脂肪堆积提供燃料[23]。随之会出现葡萄糖和脂毒性,共同促进肝脏炎症和肝窦内皮细胞毛细血管化,导致肝星状细胞活化,从而推动肝纤维化进展[24]。

几种脂肪因子脂联素、脂肪细胞脂肪酸结合蛋白(AFABP)、Gremlin-1与NAFLD和T2DM的发病机制有关[25]。脂联素是由脂肪组织分泌,其作用与NAFLD、T2DM及动脉粥样硬化的发生密切相关。脂联素可以通过提高过氧化物酶体增殖激活受体(PPAR-α)mRNA的表达,抑制TNF-α的表达,脂联素还可以抑制TNF-α诱导的NF-κB信号通路的激活,然后使TNF-α所致的炎症反应受到抑制[26]。在肝脏中,脂联素还可通过激活AMPK及PPAR-α通路,促进脂肪酸氧化并降低脂肪生成,增加胰岛素敏感性,改善IR[27]。AFABP在巨噬细胞中高度表达,包括肝脏中的Kupffer细胞[28]。循环AFABP水平升高与代谢综合征有关,包括中心性肥胖、IR、高血压和致动脉粥样硬化,并且是T2DM发展的独立预测因子[29]。作为一种促炎性脂肪因子,经活检证实的NAFLD患者的循环AFABP水平也与小叶炎症和纤维化阶段相关。最近的一项研究表明,肝纤维化小鼠肝窦内皮细胞中的AFABP表达增加。AFABP通过增强肝星状细胞中转化生长因子β-1的产生来增强肝窦内皮细胞毛细血管化和增强肝纤维化[30]。研究发现Gremlin-1会损害脂肪组织、肌肉和肝细胞中的胰岛素信号传导和作用,在T2DM患者中观察到血清水平较高。此外,在T2DM患者中,活检证实的NASH患者的肝脏Gremlin-1信使核糖核酸表达明显高于孤立性肝脂肪变性患者[31]。

2.3肠道菌群的改变

肠道菌群失调破坏肠道屏障促进细菌内毒素进入肝脏,并加剧炎症过程和NAFLD发病机制中的脂肪堆积[32]。不健康的生活方式(例如,高脂肪、低纤维饮食)会改变肠道中的微生物群定植,增加肠道通透性,并产生各种促炎因子,如LPS、TMAO、SBA 和细菌16sDNA。这些促炎因子会加重肝脏炎症和纤维化,并可能加速NAFLD的进展。短链脂肪酸(SCFAs)通过激活肠道和脂肪组织中的G蛋白偶联受体,如GPR41和GPR43[33]。GPR43激活会抑制脂肪细胞分化,增加肝脏脂肪生成,从而促进NAFLD的发展。T2DM患者肠道屏障功能受损,黏膜通透性增加,导致LPS吸收增加,LPS通过激活TLR4和TLR9,释放大量促炎细胞因子(如TNF-α、IL-1β和IL-6)和趋化因子(CCL2、CXCL2、CXCL10和CXCL16),介导肝脏的炎症和病理损伤[34]。LPS除了介导炎症反应外,还会导致严重的代谢变化,例如增加脂肪消耗,升高循环游离脂肪酸(FFA)促进NAFLD的发展。少量SBA会降低FXR活性并增加体内炎症；大量的SBA会产生大量的ROS,导致细胞DNA损伤,并导致HCC的发展[35]。

3 NAFLD治疗

目前尚无批准专门用于治疗NAFLD的药物。主要是通过控制危险因素(糖尿病、肥胖、血脂异常)、改变生活方式、限制热量摄入、减轻体重以及运动。生活方式改变、运动、控制体重是治疗NAFLDA的首要及基础。严格限制总热量、诱发酮症或减少游离糖摄入可以增强肝脏保护,地中海饮食(MD)是NAFLD最常见的饮食干预治疗策略。MD一方面改善肥胖和内脏脂肪,减少肝脂肪变性,从而改善NAFLD患者的症状[36]。另一方面改善IR,进而改变NAFLD患者的疾病状态。除饮食干预外,运动是主要方式,抗阻力运动可以减轻肝脏脂肪堆积[37]。减重可以改善NASH患者的肝脏组织学情况,研究表明,体重减轻5%可减少脂肪变性,减轻10%可改善NASH组织学和纤维化,此外还可以改善T2DM,血脂异常,降低心血管事件的发生率。由于T2DM是NAFLD的独立危险因素,目前临床上常用抗糖尿病药物治疗NAFLD,其中主要有GLP-1受体激动剂(利拉鲁肽、司美格鲁肽等)[38]、SGLT2i(达格列净),这些药物可以减轻T2DM患者的体重,改善IR,改善肝酶水平,保护肾单位,减少心血管事件,SGLT2i还可以改善T2DM患者的脂肪变性和纤维化[39]。噻唑烷二酮类(吡格列酮(PPAR-γ激动剂)。一项荟萃分析表明,吡格列酮可以显著改善糖代谢、有效减少肝纤维化和NASH[40]。常见的副作用是体重增加、水肿以及骨折。在无禁忌症情况下,吡格列酮是唯一可以用于NASH治疗的糖尿病药物。一些新型药物,例如：甲状腺受体β(TR-β)激

动剂,被证明可以改善肝脂肪变性[41],并且还可以降低LDL-c和甘油三酯浓度。成纤维细胞生长因子类似物FGF19和FGF21[42],可以改善肝脏脂肪浸润、炎症和纤维化。

4 总结与展望

综上所述,NAFLD已经成为当前全球重要的公共健康问题之一,其疾病的发生与发展与T2DM、肥胖等代谢疾病密切相关。T2DM是NAFLD的独立危险因素,反之亦然。两者协调作用,相互共存,形成恶性循环。其发病机制主要与IR、脂肪组织障碍和炎症反应、氧化应激和内质网(ER)应激、肠道菌群改变、脂毒性有关。目前临床上尚无用于治疗NAFLD的特效药,治疗方式主要是通过控制危险因素、改变生活方式、减轻体重、限制热量摄入,运动及药物治疗。因此,及时了解疾病发病机制有利于针对性研发相关治疗。

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