

肝脏脂肪变性对慢性乙型肝炎影响的研究进展

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背景资料

当前, 肝脏脂肪变性在全球范围内发病率不断增高并且呈低龄化的趋势。乙型病毒性肝炎是威胁人类健康的重大疾病之一, 乙型肝炎病毒感染在全世界范围内很广泛, 其患者部分发展成慢性肝炎, 亦有少部分可发展成肝硬化或肝癌, 成为致死的原因。

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Influence of hepatic steatosis on chronic hepatitis B

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Abstract

Worldwide, nonalcoholic fatty liver disease (NAFLD) has a high prevalence with the rising rates of overweight and/or obesity. Chronic hepatitis B (CHB) virus infection is another common cause of infectious liver diseases. In practice, the overlap between NAFLD and CHB is rather common. In this review, we summarize the relationship between NAFLD and CHB, the influence of NAFLD on CHB, and the role of the metabolic syndrome in the development of hepatic fibrosis, cirrhosis and hepatocellular carcinoma. Recent advances in understanding the reason CHB is prone to overlap NAFLD will be discussed. The adverse effects caused by NAFLD on the treatment and progression of CHB will be also elucidated. NAFLD overlapping CHB often raises a great challenge to the clinicians, in terms of diagnosis or treatment. Therefore, appropriate management of this complex situation is needed.

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Key Words: Hepatic steatosis; Chronic hepatitis B; Metabolic syndrome; Double damage

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摘要

近年来, 随着体质量超标和/或肥胖发病率的增高, 非酒精性脂肪性肝病(nonalcoholic

fatty liver disease, NAFLD)的发病率呈上升趋势。慢性乙型肝炎(chronic hepatitis B, CHB)病毒感染是另一种常见的慢性肝病。事实上, NAFLD合并CHB在临床上非常常见。在本文中, 我们概述了NAFLD和CHB的关系, NAFLD对CHB的影响, 以及代谢综合征在肝纤维化、肝硬化以及肝细胞癌的发展过程中所发挥的作用。此外, 本文还将讨论关于CHB易于合并发生NAFLD原因的最新进展。同时探讨NAFLD对CHB治疗的不利影响。NAFLD合并CHB患者肝功能异常原因的诊断和治疗对临床医生来说是一个难点。并且, NAFLD合并CHB时肝脏承受双重打击, 进行适当的治疗和管理显得尤为重要。

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关键词: 肝脏脂肪变性; 慢性乙型肝炎; 代谢综合征; 双重打击

核心提示: 代谢综合征可促进慢性乙型肝炎(chronic hepatitis B, CHB)相关性肝纤维化、肝硬化及肝癌的发生和发展, 肝脏脂肪变性影响CHB抗病毒疗效, 肝脏脂肪变性和病毒性肝炎双重打击致使肝病治疗病毒学及生化学应答率降低, 加剧纤维化进展, 抗病毒与保肝治疗亟需重视, 不可偏废。

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0 引言

非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)是指除外酒精和其他明确的肝脏损害因素所致的, 以显微镜下弥漫性肝细胞大泡性或者小泡性脂肪变性为主要特征的临床综合征。全世界范围内, NAFLD在普通人群中的发病率呈逐年升高的趋势。近年来, 随着对本病的认识, 普遍认为NAFLD是一种导致机体稳态失衡的遗传、环境、代谢应激相关的肝病。胰岛素抵抗在NAFLD的发生中发挥着重要的作用。慢性乙型肝炎(chronic hepatitis B, CHB)病毒感染在亚洲和非洲的发病人数最高, 可达240万例^[1]。CHB曾经是亚洲最常见的慢性肝病。由于NAFLD和CHB都有着非常高的发病率, 依此看来, 这两种疾病

同时发生似乎也是合理的。根据Pais等^[2]的报告, CHB患者中肝脏脂肪性变>5%的比例达到21%。临床中, 轻度CHB患者和NAFLD患者通常都会出现转氨酶升高, 并且以丙氨酸氨基转移酶(alanine aminotransferase, ALT)升高更为明显, 常不伴随其他异常。由于NAFLD和CHB缺乏特征性临床表现, 因此未经组织学鉴定, 在同时患有NAFLD和CHB的患者身上无法确定哪种疾病是引起转氨酶升高的主要原因。然而, 无论是CHB抑或NAFLD均需长期治疗和管理, 明确的诊断和适当的管理是非常必要的。

1 流行病学依据

在欧洲和美国, NAFLD是当前导致慢性肝病的最常见原因。在美国, 一项以人群为基础的研究^[3]表明, NAFLD在慢性肝病中所占的比例已经从1988-1994年的46.8%, 上升到1999-2004年的62.84%, 并进一步达到2005-2008年的75.1%。NAFLD患病率亦从5.51%升高至11.01%^[3]。与西方一致, 在亚洲, NAFLD也是很常见并且重要的疾病^[4]。中国^[5,6]、韩国^[7,8]和中国台湾^[9,10]的观察数据亦提示, 在过去的十年里NAFLD在亚洲人群中有着相似的高患病率(11%-45%)。同时, NAFLD在肥胖儿童和青少年中患病率更高(>50%)^[11,12]。

最近研究^[13]表明, NAFLD可与许多危险因素相关联。NAFLD进展虽较缓慢, 但亦可发展成肝硬化、肝功能衰竭以及肝细胞癌(hepatocellular carcinoma, HCC)^[13]。非酒精性脂肪性肝病(nonalcoholic steatohepatitis, NASH)是NAFLD的一种更严重形式。以人群为基础的研究表明, 美国6%-8%的成年人患有NASH^[14]。有些NASH患者最终会发展成肝硬化和/或肝细胞癌, 且最终将死于肝脏相关疾病^[15-17]。

据估计, 当前全世界约有20亿例被乙型肝炎病毒(hepatitis B virus, HBV)所感染, 这与慢性肝炎、肝硬化以及HCC的发生有明显相关性^[18,19]。美国HBV感染率较低为0.36%(1988-1994年), 0.33%(1999-2004年)以及0.34%(2005-2008年)^[3]。在中国, CHB是一种较常见的慢性肝病, 肝脏脂肪变性常与之同时发生^[20]。一项研究^[21]发现, 在CHB合并脂肪肝的患者中, 体质量指数(body mass index, BMI)、腰臀围比、空腹血糖以及甘油三酯和胆固醇

■ 研究前沿

目前, 病毒性肝炎合并肝脏脂肪变性正呈现高态势, 肝脏脂肪变性对合并病毒性肝炎的治疗及进展均会产生诸多不利影响, 给肝脏疾病的治疗带来了极大挑战, 需要抗病毒与保肝治疗联手, 共同抗击合并发生的肝脏疾病。

■ 相关报道

许多学者研究了肝脏脂肪变性与病毒性肝炎合并发生时, 对病毒性肝炎的治疗及预后会有哪些影响, 以此来指导肝脏疾病的治疗, 力求获得最佳疗效。

■ 创新盘点

随着病毒性肝炎合并肝脏脂肪变性发病率的增高, 针对肝脏脂肪变性对病毒性肝炎的进展, 治疗效果和预后等方面影响的报道研究也增多, 文章较多, 较杂, 本文即对相关研究做一梳理。

等指标对慢性肝病的结局有着重要影响。Wong等^[22]研究发现, CHB合并代谢综合征者发展为肝硬化的风险大于单纯CHB的患者。然而, 慢性HBV感染似乎可抑制高甘油三酯血症、脂肪肝, 以及代谢综合征的出现, 这得到中国香港进行的一项人群横断面研究的支持^[23]。

2 慢性病毒性肝炎与肝脏脂肪变性共患率高

数项研究显示^[20,24-31], CHB患者中合并脂肪肝比例相当高, 可能高达25%。一项Meta分析^[32]显示, 中国大陆脂肪肝患病率高达20.09%。30%-70%慢性丙型肝炎患者存在肝脂肪变性^[33-35]; 5%-76%(平均达28%)CHB患者肝脏病理检查存在肝脂肪变性^[36]。Pais等^[2]研究发现肝脏脂肪变性(>5%)在CHB、CHC以及NAFLD中的发生率分别为21%、43%和82%($P<0.001$); 胰岛素抵抗指数(homeostasis model assessment for insulin resistance, HOMA-IR)(评估胰岛素抵抗的常用指标)在CHB、CHC以及NAFLD中逐渐增加, 分别为: 2.3 ± 1.8 , 3.0 ± 2.6 和 3.8 ± 2.7 ($P<0.001$)。2014年的一项研究^[37]显示, 欧洲及中东地区CHB合并脂肪肝的比例最低为18%, 最高达到62%, 亚太地区的数据与此类似, 最低为14%, 最高达71%。以上研究显示CHB、CHC患者中合并NAFLD均相当常见。

3 代谢综合征促进CHB相关性肝纤维化、肝硬化

香港中文大学的一项研究^[22]提示, 代谢综合征可增加CHB患者肝硬化风险。代谢综合征、向心性肥胖和高密度脂蛋白(high density lipoprotein, HDL)过低对CHB患者肝纤维化进展的相对危险度分别为2.0、2.0和1.9。另一项研究^[38]也得出类似的结论: 向心性肥胖, 甘油三酯升高, 低HDL以及空腹血糖升高对CHB患者肝纤维化进展的相对危险度分别为7.1、6.2、5.2以及4.3。Petta等^[39]进行了一项调查肝脂肪变性与CHB/CHC患者纤维化程度的相关性, 研究各纳入170例CHB和CHC患者, 评价肝脂肪变性及IR在CHB及CHC患者中的流行及相关因素情况, 并评估肝脂肪变性程度和IR与肝纤维化严重程度的关联性。结果提示: 肝脂肪变性($\geq 10\%$)与CHB/CHC患者纤维化程度独立相关。

代谢综合征还可以促进CHB相关性肝硬化的进展。香港一项研究^[22]发现, 随着代谢综合征组份个数的增加, CHB患者肝硬化进展的相对危险度逐渐增加。代谢综合征的组份包括: 肥胖、高血压、血脂紊乱和2型糖尿病。

4 代谢综合征促进CHB相关性肝癌

台湾学者进行了一项纵向研究(REVEAL研究的一个分支)^[40], 对1142例患者进行了平均7.8年的随访。结果发现基线胰岛素水平升高是肝硬化、肝癌发生率升高的独立预测因素。来自台湾的另一项研究也发现代谢综合征可以促进CHB相关性肝癌的发生^[41]。该项研究对23567例患者进行了长达14年的前瞻性观察。假定乙型肝炎表面抗原(hepatitis B surface antigen, HBsAg)/抗丙型肝炎病毒(hepatitis C virus, HCV)双阴性, 并且BMI<30 kg/m²者HCC发生的相对危险度为1, 则HBsAg阳性并且抗HCV阴性者HCC发生的相对危险度如下: BMI<30 kg/m²伴有糖尿病, $RR = 43.0(19.3-96.1)$; BMI ≥ 30 kg/m²伴有糖尿病, $RR = 264.7(35.2-1993.0)$ ^[41]。

5 CHB容易合并脂肪肝的可能机制

为什么CHB容易合并发生脂肪肝? 实验数据^[37]表明, HBx蛋白可能诱导肝脂肪在分子水平上蓄积。Kim等^[42]进行转基因小鼠实验亦提示HBx蛋白可以诱导脂肪肝。HBx蛋白诱导PPAR- γ 表达, 激活PI3K/AKT通路, 并下调PTEN表达。HBx还可干扰胰岛素信号通路, 表现为: 下调胰岛素受体底物1(insulin receptor substrate 1, IRS1)表达, 增强细胞因子信号转导蛋白抑制剂表达并诱导IRS1泛素化^[42]。但HBV基因型对肝脂肪变性没有影响^[43]。

6 脂肪肝对CHB治疗结局的影响

研究发现, 肝脏脂肪变性可影响到CHB^[36]及CHC^[44]的治疗结局。表现为代谢综合征可推迟CHB患者血清乙型肝炎e抗原(hepatitis B e antigen, HBeAg)的天然清除^[45]。一项前瞻性队列研究^[45], 观察413例未经治疗的HBeAg阳性CHB患者出现HBeAg自然清除时患者的年龄。发现合并前代谢综合征以及代谢综合征患者HBeAg自然清除时患者年龄为44岁 ± 12 岁以及53岁 ± 7 岁, 而未合并前代谢综合征以

及代谢综合征组则为37岁±9岁(P 值均 <0.01)。校正病毒载量、抗病毒治疗以及肝内坏死性炎症后, 多变量分析提示基线时代谢综合征以及2型糖尿病是HBsAg自然清除延迟的预测因子^[45]。

脂肪肝还可影响核苷类似物抗CHB的疗效^[46]。研究^[46]显示, 合并脂肪肝的CHB患者接受恩替卡韦作为初始抗病毒方案时, HBV DNA清除率在治疗24、48以及96 wk均显著低于未合并脂肪肝的CHB患者。

基于以上肝脏脂肪变性与CHB之间有着错综复杂的相关作用, 并且对CHB的治疗及预后存在诸多影响, 相关指南及共识均给出推荐意见。2014年《肝脏炎症及其防治专家共识》认为抗炎保肝治疗是肝脏炎症综合治疗的一部分, 不能取代抗病毒等病因治疗; 反之, 抗病毒等病因治疗在病因控制前亦不能取代抗炎保肝治疗^[47]。2010年《非酒精性脂肪性肝病诊疗指南》对合并嗜肝病毒现症感染或其他肝病者, 建议根据疾病活动度和病程、药物效能等合理选用抗炎保肝药物^[48]。因此, 病毒性肝炎合并脂肪肝应抗病毒与抗炎保肝治疗并行^[36,49,50]。

7 结论

CHB合并脂肪肝患病率高, 代谢综合征可促进CHB相关性肝纤维化、肝硬化及肝癌的发生和发展, 肝脏脂肪变性影响CHB抗病毒疗效, 影响CHB, CHC的结局。双重打击致使肝病治疗面临诸多挑战: 治疗病毒学及生化学应答率降低, 加剧纤维化进展, 抗病毒与保肝治疗亟需重视, 不可偏废。

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应用要点

本文主要梳理了近年来病毒性肝炎合并肝脏脂肪变性的流行趋势, 以及肝脏脂肪变性对病毒性肝炎的进展, 治疗效果和预后等方面影响的报道, 为本领域研究者梳理文献, 提出展望, 同时为病毒性肝炎合并肝脏脂肪变性的诊治提供重要依据。

■ 名词解释

代谢综合征: 是指人体的蛋白质、脂肪、碳水化合物等物质发生代谢紊乱的病理状态, 是一组复杂的代谢紊乱症候群, 其病因尚未明确, 目前认为是多基因多种环境因素相互作用的结果, 与遗传、免疫等关系密切。

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同行评价

本文较好的综述了非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)和慢性乙型肝炎(chronic hepatitis B, CHB)的关系, NAFLD对CHB的影响,以及代谢综合征在肝纤维化、肝硬化以及肝细胞癌的发展过程中所发挥的作用。此外,本文还讨论了关于CHB易于合并发生NAFLD原因的最新进展,同时探讨NAFLD对CHB治疗的不利影响。所引用文献较新,杂志较权威,总结的观点客观准确。

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