世界华人消化杂志®
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世界华人消化杂志 2013年9月28日; 21(27): 2759-2764
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

述评 EDITORIAL

代谢综合征与慢性肝病

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收稿日期: 2013-05-27 修回日期: 2013-07-05
接受日期: 2013-08-29 在线出版日期: 2013-09-28

Metabolic syndrome and chronic liver diseases

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Received: 2013-05-27 Revised: 2013-07-05
Accepted: 2013-08-29 Published online: 2013-09-28

Abstract

Drastic changes in diet and lifestyle as well as rapid population aging in China have made the morbidity of metabolic syndrome (MetS) quite close to the levels of industrialized countries. MetS is one of the highest risk factors for cardiovascular diseases; accumulating epidemiological data also show that MetS is an independent risk factor of the development of chronic liver cirrhosis and hepatocellular carcinoma. The synergism between MetS and HBV infection is considered to robustly increase the morbidity and mortality of end-stage liver diseases, and this needs particular attention because of the huge HBV-positive population in China. The purpose of this review is to disucss the association between MetS and the development of end-stage liver diseases.

Key Words: Metabolic syndrome; Non-alcoholic fatty liver disease; Chronic liver cirrhosis; Hepatocellular carcinoma

Shi YJ, Bu H, Metabolic syndrome and chronic liver diseases. Shijie Huaren Xiaohua Zazhi 2013; 21(27): 2759-2764 URL: http://www.wjgnet.com/1009-3079/21/2759.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i27.2759

摘要

饮食结构和生活方式的剧变以及日益突出的人口老龄化, 使我国代谢综合征(metabolic syndrome, MetS)发病率已相当接近工业化国家水平. MetS是罹患心脑血管疾病的高危因素, 而越来越多的流行病学资料显示MetS还是导致慢性肝硬化及肝细胞肝癌的独立危险因素. 加之我国HBV携带者人数众多, 如果合并MetS势必将加大患者发生终末期肝病的风险, 尤其需要引起高度重视. 本文将就MetS与慢性终末期肝病的相关性进行阐述.

关键词: 代谢综合征; 非酒精性脂肪性肝病; 慢性肝硬化; 肝细胞肝癌

核心提示: 代谢综合征(metabolic syndrome, MetS)是慢性终末期肝病的独立危险因素, 其发病率在我国已接近工业化国家和地区, 加之乙型肝炎病毒(hepatitis B virus)的高携带率, 使罹患慢性肝病的高风险人口基数相当惊人. 有必要开展大规模临床试验并加强基础研究, 阐明MetS患者发生慢性肝病的高危因素并深入探讨其机制, 尤其是本身具有基础肝病者.

石毓君, 步宏. 代谢综合征与慢性肝病. 世界华人消化杂志 2013; 21(27): 2759-2764 URL: http://www.wjgnet.com/1009-3079/21/2759.asp DOI: http://dx.doi.org/10.11569/wcjd.v21.i27.2759

■背景资料
越来越多的临床研究发现MetS是慢性终末期肝病的独立危险因素. 随着人口老龄化和饮食结构的改变, 我国居民罹患MetS的人口比例已相当接近欧美工业化国家水平, MetS在导致国民慢性终末期肝病中的作用需要得到足够重视.

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本文介绍了MetS的定义和流行病学资料，重点综述了MetS作为慢性终末期肝病的独立危险因素的临床研究证据，简要介绍了MetS导致慢性终末期肝病的机制及其干预措施.

0 引言

多种原因可导致肝细胞损伤, 因肝细胞本身再生能力极强, 一些急性损伤可通过肝再生短期内使肝细胞数量和功能完全恢复[1-3]. 乙型肝炎病毒(hepatitis B virus, HBV)或丙型肝炎病毒(hepatitis C virus, HCV)感染、长期肝毒性物质(如酒精)暴露等, 肝脏遭受持续性损伤, 则常发展为慢性进行性肝病. 至终末期, 多表现为肝纤维化、肝硬化甚至原发性肝细胞肝癌(hepatocellular carcinoma, HCC). HBV的持续感染和迁延不愈是引起国人肝病慢性进行性发展及HCC的最主要因素[4-6]. 而在欧美工业化国家, HCV感染是引起慢性终末期肝病的首要原因, 但在美国仅约半数HCC与病毒感染或长期酗酒有关, 另有20%-50%HCC病因不清[7]. 越来越多的大样本临床试验发现, 与病毒感染并无直接关联的众多因素可能是肝硬化及HCC发生的独立危险因素. 其中最为重要的就是代谢综合征(metabolic syndrome, MetS)[8-14].

1 代谢综合征的定义及流行病学

MetS是多种代谢成分异常聚集的病理状态, 是一组复杂的代谢紊乱症候群, 临床表现为中心性肥胖、血压升高、糖耐量降低或糖尿病、血脂水平紊乱, 是导致糖尿病(diabetes mellitus, DM)、心血管疾病(cardiovascular diseases, CVD)的危险因素. 随着研究的深入, 目前MetS涵盖的范畴越来越多, 还包括多囊卵巢综合征、高胰岛素血症或高胰岛素原血症、高纤维蛋白原血症和纤溶酶原激活物抑制物-1增高、高尿酸血症、内皮细胞功能紊乱-微量白蛋白尿和炎症等. 胰岛素抵抗(insulin resistance, IR)可能是MetS的最主要原因. IR指正常数量的胰岛素不足以产生对脂肪细胞、肌肉细胞和肝细胞正常的胰岛素响应的状况, 故MetS又可称为“胰岛素抵抗综合征”[15,16]. 2005年国际糖尿病联盟(International Diabetes Federation, IDF)颁布了MetS诊断标准: 中心性肥胖(西方男性和女性腰围分别≥94 cm和≥80 cm, 华人男性和女性腰围分别≥90 cm和≥80 cm)且符合以下2项者, (1)高密度脂蛋白(high density lipoprotein, HDL)-C: 男性<1.04 mmol/L、女性<1.29 mmol/L, 或已接受相应治疗; (2)TG>1.7 mmol/L或已接受相应治疗; (3)血压≥130/85 mmHg, 或已接受相应治疗; (4)空腹血糖≥5.6 mmol/L, 或此前已诊断为2型糖尿病. 根据上述标准, 美国20岁以上成年人中约有40%可诊断为MetS患者, 男性略多于女性[17]. 在饮食结构和生活方式骤变, 人口老龄化日益突出的当下, 我国MetS患者人数骤升. 中国疾控中心2008年报道为6000万例, 中华医学会糖尿病分会2008年对14省市调查显示, 男女性患病率分别为16.7%和11.7%, 而WHO数据显示香港地区发病率更是高达21%.

MetS受累器官众多, 非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)被认为是MetS的肝脏组份(NAFLD is the hepatic component of metabolic syndrome). 综合多个中心发表的数据, 工业化国家和地区(其中一个数据来自上海市)NAFLD患者已超过成年人口的1/3, 位居各种肝病的首位[18-20], 也是导致慢性终末期肝病的最重要原因[21]. 中国内分泌协会近期报道, 国人NAFLD患病率约为15%-30%[22]. 越来越多的证据表明, 美国的那些20%-50%病因不清的HCC患者就多由NAFLD及其继发的非酒精性脂肪性肝炎(nonalcoholic steatohepatitis, NASH)引起. NASH引起的终末期肝病是目前美国肝移植的第3位原因, 预计到2020年将成为肝移植的首要原因[23,24].

2 代谢综合征是肝硬化的独立危险因素

NAFLD如合并病毒感染将加速病情进展. 30%-70%的慢性丙型肝炎(chronic hepatitis C, CHC)患者伴有肝脂肪变, 其进展为肝硬化的速度加快, 同时对聚乙二醇干扰素和利巴韦林治疗的病毒学应答明显降低, 与HCV基因型无关[25]. 基因1型和4型HCV感染者, IR与高病毒载量和严重的肝硬化相关; 基因3型HCV则可直接导致肝脂肪变[26]. 国人终末期肝病90%以上为HBV相关性[27], MetS是否参与了慢性肝硬化发生发展呢？来自杭州[28]和台湾[29]的两项大规模临床研究观察了慢性乙型肝炎(chronic hepatitis B, CHB)和MetS的关系. 在杭州(n = 7437)和台湾(n = 53528)的HBsAg阳性者中的MetS患病率分别为11.5%和12.6%, 略低于对照人群. 肝脂肪变与体质量指数(body mass index, BMI)、腰围、糖尿病和血脂异常等多个MetS指标相关, 而病毒因素(HBeAg状态和HBV DNA载量)并不是CHB患者肝脂肪变发生的危险因素. CHB似乎并不增加患MetS的风险, 那么MetS是否增加CHB患者肝纤维化的风险呢？杭州的试验发现伴MetS的CHB患者51%出现“可能的肝硬化”, 无MetS者仅为29%; “很可能的肝硬化”在有和无MetS者中分别为24%和11%. 在接受肝活检的

病例中, 伴MetS者39%为肝硬化, 而无MetS者仅为11%. 香港中文大学通过对1466例CBH患者进行前瞻性队列研究也证实了MetS是CBH患者肝硬化的独立危险因素, 伴发MetS者罹患肝硬化的风险更高, MetS组分越多者肝硬化的风险越大[30].

3 代谢综合征与HCC发生发展密切相关

美国近期开展的一项临床试验中, 纳入了16448例HCC患者(有效病例数为3649)和195953例健康对照, 结果显示HCC患者中MetS发病率明显高于普通人群(37.1% *vs* 17.1%), 校正多因素回归分析表明MetS显著增加了罹患HCC的风险[31]. 北欧一项纳入578700例成年人的前瞻性试验中发现, BMI、血糖水平以及MetS综合评分(composite MS score)与HCC发生率成正相关[32]. 人们已经注意到IR或MetS与HCV感染相关HCC密切相关[33,34]. 国内东方肝胆外科医院最近报道, 在179例HBV相关HCC患者中, 其平均BMI、血糖、胰岛素水平和胰岛素抵抗明显高于对照组[35]. 有报道指出肥胖使罹患HCC的风险增加2-5倍, 远高于肥胖对其他肿瘤的影响[36]; 而糖尿病则能使该风险增加一倍. 台湾的一个研究报道甚至认为肥胖与糖尿病能成百倍地增加HBV/HCV感染者罹患HCC的风险[37]. 此外, 多项临床试验还证实了MetS中的多个独立指标(如尿酸水平), 与肝硬化和HCC的发生发展密切相关[38,39]. MetS患者发生HCC时可能并无明显的肝硬化改变[40-42]. MetS甚至可以影响HCC患者的预后, 伴MetS者发生肿瘤转移、复发的可能性增大, 其原因可能与浸润转移相关信号通路的激活有关. 可见, 以MetS为主的多种复杂因素参与了肝病慢性进行性过程, 与HCC发生、发展及预后密切相关.

4 代谢综合征致肝细胞损伤机制及干预

MetS的肝损伤主要表现为NAFLD及NASH, 随着病程进展, 肝细胞发生脂肪变性, 严重者出现肝细胞坏死, 进而导致坏死性炎症, 肝细胞代偿性增殖, 纤维组织增生, 肝脏组织结构被破坏重构, 最后发展为肝纤维化甚至HCC[43]. 人们普遍用所谓“二次打击”甚至“多重打击”学说来解释NAFLD[44-47]: 肝细胞脂肪变性, 饱和游离脂肪酸(free fatty acids, FFA)、游离胆固醇(free cholesterol, FC)、超长链多不饱和脂肪酸(polyunsaturated fatty acid, PUFA)等过度沉积; 由于脂肪变性的肝细胞活力下降, 产生的氧化代谢产物增多引发氧化应激, 直接或间接地激活JNK信号通路或者线粒体/溶酶体细胞死亡通路, 使得脂肪变性的肝细胞发生坏死; 进而肝脏内非实质细胞(Kupffer细胞、肝星状细胞、内皮细胞等)活化, 分泌大量细胞因子或炎症介质, 肝组织出现炎症、坏死甚至纤维化. 事实上, MetS时肝细胞还受到肝外有害因素的攻击. 内脏脂肪被认为是肿瘤坏死因子-α、巨噬细胞趋化蛋白(macrophage chemoattractant protein-1, MCP-1)等炎症介质的重要来源. 此外, 循环中的淋巴细胞释放的大量炎症介质以及肠源性内毒素等都可能通过先天性免疫系统, 参与肝细胞损伤.

MetS所致肝损伤的治疗仍然缺乏特异有效的手段, 目前主要采取系统性治疗方案, 如减体质量、体育锻炼、改变饮食习惯、控制血糖、改善胰岛素抵抗、降血脂等. 此外, 平衡肝细胞脂代谢、抑制氧化应激反应、抑制炎症反应、改善肠道菌群等的策略也成为研究热点[44,48-53].

5 结论

肝脏通常仅仅被看作是MetS的靶器官. 然而, 肝脏是糖、脂肪、蛋白质3大营养物质的代谢中心. 肝细胞功能的异常将直接导致多种营养物质的代谢障碍. IR是MetS的核心事件, 其本身就包括了肝细胞自身IR: 肝细胞表面胰岛素受体(insulin receptor, InsR)下调, 合成存储糖原能力下降进而导致血糖升高. 因此肝细胞的病变也极可能是引起MetS的重要原因[54,55]. NASH甚至被看作是MetS的使动因素[56]. 肝脏在MetS发生发展中的作用目前还知之甚少，值得深入探讨.

在饮食结构、生活方式发生巨大变化和人口老龄化日益突出的当下, 我国MetS患者人数激增, 单独罹患2型糖尿病、高血压、血脂紊乱的人口数量均超过1亿例. 近年来美国HCC发病率并未随着HCV感染者数量的下降而下降, 反而逐年上升, MetS成为其中最主要原因. 我国MetS发病率已相当接近工业化国家水平, 加之HBV感染者人数众多, 这些高危因素的共同存在使罹患慢性肝病的高风险人口基数相当惊人. 目前国内已开展的临床试验纳入病例数还较少, 尤其对无病毒感染的MetS患者发生慢性肝病的重视程度还非常薄弱. 有必要开展大规模的临床试验和加强基础研究, 阐明MetS患者发生慢性肝病的高危因素并深入探讨其机制, 尤其是本身具有基础肝病者.

■相关报道

国外关于MetS所致慢性肝病研究报道较多. 国内范建高等于第三届全国肝病治疗进展与临床药学学术研讨会(2009年)上介绍了《代谢综合征、非酒精性脂肪性肝病与慢性乙型肝炎》, 2013年在中华肝脏病杂志发表了《加强代谢综合征与肝病关系及其对策的研究》.

■创新盘点
已有不少研究性论文报道了MetS与慢性终末期肝病的相关性, 本文首次对这些报道进行了综述, 并结合国内研究现状, 介绍了MetS合并乙型肝炎病毒(hepatitis B virus)感染对慢性终末期肝病的影响.

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■应用要点
本文有助于读者了解MetS在慢性肝病发生发展中的地位, 呼吁更多临床医生和科研工作者重视MetS对肝脏的危害, 加强相关研究.

■同行评价
本文引用最新的文献阐述了代谢综合征与慢性肝病的关系研究现状, 为该领域的研究做了较好的总结并提出展望, 具有一定指导意义.

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编辑 田滢 电编 鲁亚静

ISSN 1009-3079 (print) ISSN 2219-2859 (online) DOI: 10.11569

• 消息 •

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本刊讯 一年一度的中国科技论文统计结果2012-12-07由中国科技信息研究所(简称中信所)在北京发布.《中国科技期刊引证报告(核心版)》统计显示, 2011年《世界华人消化杂志》总被引频次3871次, 影响因子0.775, 综合评价总分65.5分, 分别位居内科学类52种期刊的第5位、第7位、第5位, 分别位居1998种中国科技核心期刊(中国科技论文统计源期刊)的第65位、第238位、第138位; 其他指标; 即年指标0.081, 他引率0.82, 引用刊数526种, 扩散因子13.59, 权威因子1260.02, 被引半衰期4.3, 来源文献量642, 文献选出率0.93, 地区分布数29, 机构分布数302, 基金论文比0.45, 海外论文比0.01.

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