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非酒精性脂肪性肝病与代谢综合征组分的相关性研究进展*

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摘要: 非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD) 在全世界人群中发病率逐年上升,成为新的全球公共健康问题,已越来越引起临床关注。其发病以胰岛素抵抗为基础,与肥胖、血脂紊乱、原发性高血压、2型糖尿病等代谢综合征各组分密切相关。NAFLD可进展至肝硬化、肝衰竭甚至肝癌,伴有代谢综合征一种或多种组分可能加速疾病的进展。NAFLD初期是一种可逆性过程,充分了解影响其发生、发展的相关代谢危险因素并及时纠正,可能导致疾病的逆转或延缓其进程。本文就NAFLD与代谢综合征各组分的相关调查研究进行综述。

关键词: 非酒精性脂肪性肝病;代谢综合征 X;胰岛素抵抗

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Advances of Correlation between Nonalcoholic Fatty Liver Disease and the Components of Metabolic Syndrome*

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ABSTRACT: Nonalcoholic fatty liver disease is increasing in population all over the world. As a new global public health problem, it arouses more and more clinical concerns and not clear its pathogenesis up to now. The onset of nonalcoholic fatty liver disease is on the basis of insulin resistance while related to components of metabolic syndrome including obesity, dyslipidemia, essential hypertension and diabetes. The disease may progress to liver cirrhosis, liver failure or liver cancer, one or more components of metabolic syndrome associated with NAFLD may accelerate the progress of the disease. Early NAFLD is a reversible process, fully understanding of the impact of metabolic risk factors on its occurrence and development and promptly correcting it, may result in disease reversal or slowing down its progression. which is a hot topic of research recently. This paper briefly reviewed the progress of the research between NAFLD and components of metabolic syndrome.

Key words: Nonalcoholic fatty liver disease; Metabolic syndrome X; Insulin resistance

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随着肥胖在全世界范围内的流行,非酒精性脂肪性肝病(Nonalcoholic Fatty Liver Disease, NAFLD)成为新的主要的公共健康问题^[1]。基于不同的评价方法,全世界普通人群中NAFLD的患病率在6%-33%之间^[2]。在我国较发达的地区,非酒精性脂肪性肝病的社区患病率大约是15%^[3]。

印度一项研究评价非肥胖NAFLD患者中代谢综合征(Metabolic Syndrome, MS)和胰岛素抵抗(Insulin Resistance, IR)的发生率,结果显示30%的NAFLD患者合并MS,97.5%的NAFLD患者有IR,提示IR普遍存在于MS中,并且在非肥胖NAFLD患者的发病中扮演重要角色^[4]。MS以内脏性肥胖、血脂异常、高血压、胰岛素抵抗或糖尿病为特征,在肥胖、糖尿病以及具有其他MS特征的患者中,NAFLD比较普遍,所以NAFLD被认为是MS在肝脏的表现^[5]。

NAFLD疾病谱包括非酒精性单纯性脂肪肝(Nonalcoholic Simple Fatty Liver, NSFL)、非酒精性脂肪性肝炎(Nonalcoholic Steatohepatitis, NASH)、和NASH相关性肝硬化、肝癌。NASH是NAFLD的进展类型,它可以发展至肝硬化、肝衰竭以及肝癌。因为NAFLD常伴有MS,所以疾病的诊治重点就是改善总体预后,针对NAFLD伴MS患者制定和实施个体化治疗计划可能导致疾病的逆转或者延迟疾病进展至NASH。

1 肥胖与NAFLD的调查研究

基于目前不同的研究估计,多余的脂肪沉积于肝脏见于大约20%-30%的西方国家的成年人,其中有2%-3%达到NASH的诊断标准,并且最终有多达1/3的NASH成年人进展至肝纤维化甚至肝癌^[7-9]。

NAFLD是儿童最常见的慢性肝病,美国一项以学校肥胖

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青少年为基础样本的多中心实验研究发现,在 127 名肥胖青少年中,不明原因的丙氨酸氨基转移酶异常率为 23 %,其中男孩(44 %)是女孩(7 %)的 6 倍^[10]。东欧—法医学机构为调查脂肪肝变在儿童人群中的发病率^[11],对 265 名死于创伤的儿童尸检,11(4.2 %)名儿童被报道脂肪肝变性,其中 6 (54.5 %)名儿童超重。在所有 342 名儿童中,18(5.3 %)名儿童被报道脂肪肝变性,其中 10(55.6 %)名儿童超重,包含 1(0.3 %)例 NASH,由此得出结论肥胖是脂肪肝变性的一个非常重要的危险因素。日本的一项研究发现^[12],在肥胖患者和非肥胖症受试者中,肝脏脂肪变性的严重程度与内脏脂肪积累和胰岛素抵抗呈正相关,表明内脏脂肪堆积是非酒精性脂肪肝进展的一个重大危险因素,而不是身体质量指数。

越来越多的证据表明,脂肪细胞分泌的细胞因子,即脂肪因子参与 NAFLD 的致病机制及疾病进展过程。瘦素被认为参与 NASH 的二次打击,最初,它有助于 IR 的形成和脂肪变性,继之它的促炎作用起着关键的纤维化介导作用^[13]。脂联素具有削弱 IR 和保护作用,研究表明,脂联素显著改善小鼠肝脂肪变性,脂联素基因敲除的小鼠,肝脏损伤和纤维化显著增加^[14]。

2 血脂紊乱与 NAFLD 的调查研究

杨晋辉等^[15]研究显示,NAFLD 患者较正常对照组甘油三酯(Triacylglycerol, TG)和总胆固醇(Total Cholesterol, TC)均显著增高,说明脂肪肝患者存在明显的 TG 和 TC 代谢紊乱。NAFLD 患者的血脂异常特点是 TG 升高,高密度脂蛋白胆固醇(High Density Lipoprotein Cholesterol, HDL-C)降低,低密度脂蛋白胆固醇(Low Density Lipoprotein Cholesterol, LDL-C)的水平升高^[16-18]。在一项包含 16 名 NAFLD 患者和 24 名对照者的研究表明,NAFLD 与 HDL-2 降低显著独立相关^[19]。NAFLD 中脂质和脂蛋白的变化机制还不是很清楚,但它们与肝脏生产过量的极低密度脂蛋白(Very Low Density Lipoprotein Cholesterol, VLDL-C)和循环中各种脂蛋白清除下降有关^[20]。

Donnelly 等的一项研究证明,沉积在 NAFLD 肝脏的 TG 近 60 %来源于游离脂肪酸(Free Fatty Acid, FFA),26 %源于肝脏内脂肪的从头生成,而更少的 15 %来源于饮食^[21]。IR 致使 FFA 内流入肝脏增多,导致脂肪的从头合成、脂肪酸酯化、酯化脂肪酸储存于肝脏转向合成 VLDL,综合这些因素,胰岛素抵抗时有利于 TG 在肝脏内沉积,从而通过多种通路产生脂毒性,形成肝脂肪变性^[22]。

3 高血压与 NAFLD 的调查研究

近年来发现在高血压病患者中脂肪肝较一般人群明显提高,然而关于高血压和 NAFLD 的直接关系尚不明确,现有研究发现,高血压可能是 NAFLD 的一大危险因素。Alejandro 等^[23]对 454 名 50 岁以上中老年非肥胖人群进行体检,高血压组(208 人)与临界血压组(246 人)比较发现:非酒精性脂肪肝的总患病率为 38.5 %,在高血压组中 NAFLD 患病率为 49.5 %,比临界血压组的 NAFLD 患病率高 21.2 %。就相关因素进行比较得出结论:非酒精性脂肪性肝病不仅与高血压独立相关,也与临界血压的收缩压独立相关,而与舒张压没有相关性。

NAFLD 时常存在 IR, IR 与高血压的因果关系还存在争

议。多数学者认为,IR 是原发性高血压的发病因素之一,目前认为 IR 致血压升高的可能机制有下列几个方面:①交感神经系统兴奋性增加及儿茶酚胺的释放:Kern 等^[24]认为,高胰岛素血症可激活交感神经活性,使循环中儿茶酚胺增多,导致血压升高;②影响细胞膜钠泵活性:Resnick 等^[25]研究发现高胰岛素血症可抑制钠泵,导致细胞内钠水的潴留,从而使血压升高;③增加内皮素的合成:Frank 等^[26]证明高胰岛素血症和高血糖在体内可能促使内皮素释放,内皮素是一个强有力的血管收缩肽,促使血压升高;④血管内皮细胞损伤:Toutouzas 等^[27]发现,在 IR 状态下内皮源性一氧化氮产生减少,胰岛素介导的内皮细胞依赖性血管舒张功能受损,提示由于 IR 所致的内皮细胞功能异常可能是其血压升高的原因之一。

4 糖尿病与 NAFLD 的调查研究

在糖尿病人群中,NAFLD 和 NASH 的患病率分别是 60 % -70 %和 22 %^[28,29]。糖尿病不仅是 NAFLD 发生的风险因素,也是 NAFLD 发展至肝硬化甚至肝癌的风险因素^[30,31]。反过来,NAFLD 亦是糖尿病发生的一个独立危险因素,来自韩国的一项研究调查空腹血糖调节受损的 NAFLD 患者发生糖尿病的风险,NAFLD 组糖尿病的发生率是 9.9 %,而非 NAFLD 组的发生率是 3.2 %,表明 NAFLD 在发生 IR 的 T2DM 的发生中有独立累加效应^[32]。

2 型糖尿病的发病核心就是 IR, IR 是 NAFLD 的始动因素,IR 通过脂解作用和高胰岛素血症导致肝细胞内脂肪堆积已被研究证实^[33]。正常情况下,脂肪酸能被储存而不释放入血是由于受到胰岛素敏感脂酶的抑制,在糖尿病患者中由于肝脏发生胰岛素抵抗,血浆游离脂肪酸水平升高、TG 增高、HDL-C 降低,引起脂代谢紊乱,大量脂肪进入肝细胞在肝内蓄积形成脂肪沉着及肝细胞变性肿大形成脂肪肝,故肝源性胰岛素抵抗成为 NAFLD 的发病关键因素。

5 小结与展望

综上所述,NAFLD 的发生和发展与 MS 各个组分强烈相关,包括肥胖、脂代谢紊乱、高血压和 2 型糖尿病。因为 NAFLD 与代谢综合征和胰岛素抵抗相关,目前已经确认 NAFLD 是心脑血管疾病、糖尿病的独立危险因素,值得注意的是心脑血管疾病的患病率和死亡率的增加将成为更严重的后果。故作为临床医师,对于初诊 NAFLD 的患者除加强健康教育外,对它与代谢性疾病的密切关联及预后也应重新认识与评估,从而制定更个体化合理化的多层面治疗方案,进一步逆转疾病或延缓疾病的进程。

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