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文献综述 REVIEW

肠道微生态与非酒精性脂肪性肝病的相关性研究现状及临床意义

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Relationship between gut microbiota and non-alcoholic fatty liver disease

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Abstract

The incidence of non-alcoholic fatty liver disease (NAFLD) has been increasing during these years. As we understand more about gut microbiota, the relationship between gut microbiota and NAFLD has been revealed. Both animal experiments and clinical studies show that gut microbiota can not only act on NAFLD *via* the gut-liver axis and two-hit theory, but also play an important role in liver inflammation and hepatic fibrosis. Experiments also indicate that using probiotics, prebiotics, berberine and antibiotics to regulate gut microbiota can relieve inflammation, lower body mass index and improve insulin resistance, which can be a new treatment for NAFLD and other metabolic diseases.

Key Words: Non-alcoholic fatty liver disease; Gut microbiota; Probiotics

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摘要

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)的发病率近年来不断提高, 而随着对肠道微生态认知的加深, 二者的关系逐渐明确. 动物和临床实验均指出肠道菌群可通过肠-肝轴和二次打击机制促使NAFLD的发生, 并在肝炎症反应和纤维化中发挥重要作用. 通过益生菌、益生元和

背景资料
非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)发病率持续居高不下, 随着高通量测序技术的发展, 对肠道微生态的了解较过去有了很大进展, NAFLD与肠道微生态之间的联系逐渐成为研究的热点.

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研发前沿
肠道微生态具体是通过何种机制作用于NAFLD, 是否存在一种或几种细菌与NAFLD的发生发展密切相关. 益生菌制剂被用于NAFLD是否有确切的效果, 应怎样规范使用.

小檗碱及抗生素等方式调节肠道菌群可减轻患者的肝病程度, 并可调节体质量指数, 减轻胰岛素抵抗, 是治疗NAFLD等代谢性疾病的新思路.

关键词: 非酒精性脂肪性肝病; 肠道微生态; 益生菌

核心提示: 肠道微生态改变通过二次打击、肠-肝轴、引起内毒素增加、影响肠道转运、通透性等多种作用促进非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)发生, 并可促进肝炎症和纤维化反应. NAFLD患者肠道微生态可发生相应的改变. 通过调节肠道菌群可减轻肝脏炎症反应, 可成为治疗NAFLD的新思路.

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0 引言

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是指与肥胖和代谢综合征密切相关的代谢应激性肝病, 包括单纯性脂肪肝、非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)及其相关肝硬化和肝细胞癌(hepatocellular carcinoma, HCC)[1]. 近年来, 随着NAFLD发病率的增高和对肠道微生态认识的加深, 二者的关系逐渐明确, 调节肠道微生态也成为了防治NAFLD的新思路.

1 肠道微生态改变引起NAFLD的机制

目前解释肠道微生态与NAFLD关系的主要学说为“肠-肝轴”学说[2]. 门静脉为肝脏提供70%-75%的血流, 同时, 门静脉血液富含肠道产生的细菌产物、环境毒素、食物抗原等, 运送入肝脏由肝脏完成解毒、转运、免疫等多项功能. 同时也有研究[3]表明大量的饱和脂肪酸通过小肠上皮绒毛吸收入门静脉, 使循环中脂质浓度上升, 增加肝脏的代谢负担的同时, 高水平脂质本身通过其“脂毒性”升高氧化应激水平, 损害机体的脂膜系统, 引起细胞损伤和肝脏胰岛素抵抗. 临床中发现, 空肠-回肠旁路术后患者出现NAFLD的风险增加[4], 原因可能为该手术建立了肠道盲袢, 导致患者肠道细菌过度繁殖, 给与抗生素治疗或外科手术去除盲袢可逆转空-回肠旁路相关的肝损害, 由此表明肠道细菌过量繁殖与NAFLD有直接关系.

动物[5]和人体实验[6,7]均显示NAFLD发生时, 可观察到肠通透性增加和小肠细菌过度生长(small intestinal bacterial overgrowth, SIBO), 此时肝脏暴露于大量的细菌产物中, 肠道屏障受损后, 细菌易位、内毒素进入门脉系统, 激活肝脏Kupffer细胞等, 进而释放一系列炎症因子, 可导致肝细胞的炎症反应和纤维化过程[8,9]. SIBO除了通过增加肠-肝轴中的细菌代谢产物而导致NAFLD之外, 还可通过改变小肠转运功能而导致NALFD. Volynets等[10]通过测试NAFLD患者的口盲传输时间, 认为NAFLD患者同时存在的SIBO可导致小肠转运功能异常. Wu等[11]在动物实验中也有类似的发现, 即NAFLD组大鼠存在明显SIBO及小肠运动功能抑制, 且予抗生素治疗可降低大鼠谷丙转氨酶(alanine transaminase, ALT)、谷草转氨酶(aspartate transaminase, AST)水平, 提示SIBO与小肠转运功能及NAFLD的发展均有一定的关系.

肠道微生态改变可引起内毒素(endotoxin, ET)的增加[12], ET是革兰氏阴性杆菌细胞壁外膜结构即磷脂双分子层结构, 主要由脂多糖(lipopolysaccharides, LPS)组成, 是介导多种肝脏损伤的重要因素, 可通过激活TLR4等的细胞内传导信号途径、细胞因子及活性氧等, 导致肝脏病变发生发展[13]. 动物实验中, NAFLD模型小鼠可检测出明显的ET、LPS、肿瘤坏死因子-α(tumor necrosis factor α, TNF-α)和白介素(interleukin, IL)-6水平增高[14]. 同时有临床实验[15,16]表明在已被活检确诊的NAFLD患者中, ET水平较健康人对照明显增高. ET可通过细胞不良反应直接作用于肝细胞, 同时也可激活TNF及炎性因子, 引起肝细胞炎症反应及纤维化过程. 高水平TNF-α与肝损伤直接相关, 且已经脂肪变的肝脏对ET及TNF-α的损伤较正常肝细胞更敏感[17], 同时, LPS也能通过上调TNF-α转录水平, 介导鼠类NAFLD模型肝细胞凋亡的发生[18]. LPS可通过TLR4介导的信号途径活化Kuffer细胞, 引发细胞内炎症反应. 有研究[19]报道TLR4/MyD88信号通道在高脂饮食相关脂肪性肝病发病早期起关键作用.

肠道细菌过度生长可引起肠道通透性改变[20]. 有实验通过对NAFLD患者进行^{51}Cr-EDTA的排泄实验、十二指肠紧密连接蛋白的表达水平等的测定, 发现NAFLD患者肠道通透性明显升高, 且这一改变与肝脂肪变性程度有关, 进而推测肠壁上皮细胞间紧密连接蛋白异常可能导致了肠壁通透性增加, 从而在肝脏脂肪沉积发生中起重要作用[21,22]. Purohit等[23]指出肠道菌群可分解乙醇产生乙醛, 增加紧密连接和黏附连接蛋白酪氨酸磷酸化, 从而损伤肠黏膜, 引起肠壁通透性增加. 此外酒精产生的一氧化氮(nitric oxide, NO)通过与微管蛋白作用亦可导致肠壁通透性增加.

2 NAFLD发生时肠道微生态的改变

如前所述, NAFLD发生时可观察到SIBO, 同时大肠中微生态也发生改变. Bull-Otterson等[24]发现NAFLD的小鼠中拟杆菌门, 变形菌门, 厚壁菌门均较对照组小鼠有所增加. 同时有临床实验表明患NAFLD患者的粪便中肠道菌群组成与正常人在组成和数目上均有差异[20]; Mouzaki等[25]通过一个前瞻性, 横断性研究发现, NASH患者粪便中拟杆菌含量比例较低, 球形梭菌属含量较高. 同时Zhu等[26]发现NASH患者的粪便中可检测出变形菌门细菌含量的升高及厚壁菌门细菌的下降. Jiang等[27]指出, NAFLD患者的粪便标本中厚壁菌门、厌氧菌、乳杆菌等数量均较健康对照组有显著上升. Quigley等[28]发现NAFLD患者肠道中拟杆菌门下降, 变形杆菌和梭菌属数量上升.

3 通过调节肠道菌群治疗NAFLD

由于肠道菌群的数量及种类变化可参与NAFLD的发生机制, 因此通过恢复NAFLD患者肠道微生态平衡, 可减轻肠源性内毒素血症, 减少对肝细胞形成“二次打击”, 减轻肝脏炎症及纤维化作用[29,30]. 主要的手段包括应用益生菌, 益生元以及抗生素.

3.1 益生菌 益生菌指对宿主健康产生有益作用的活的微生物, 通过调节肠道菌群组成、改善肠黏膜屏障功能、消除内毒素血症以及影响胆固醇、维生素、氨基酸物质代谢、促进肠上皮细胞黏蛋白分泌及潘氏细胞sIgA的分泌等途径, 在预防和改善NAFLD发病中起重要的保护性作用.

欧洲的一项临床试验[31]显示, NAFLD患者口服3 mo益生菌后, 其ALT, AST等均可见显著下降. Vajro等[32]对20例肥胖儿童进行益生菌治疗NAFLD的随机双盲安慰剂对照试验中, 益生菌治疗组8 wk后血清ALT显著下降, 且BMI也有降低. Shavakhi等[33]报道, 在口服二甲双胍同时联用益生菌可显著提高NAFLD患者血清转氨酶的改善程度. 香港的一项临床研究[34]中将20例患者平均分为实验组及对照组, 其中实验组给予双歧杆菌及乳酸菌合剂, 用药6 mo后实验组AST及肝脂肪化程度较对照组下降明显. 杨林辉等[35]报道枯草杆菌肠球菌二联活菌胶囊可降低NAFLD患者肠道通透性以及血清内毒素和转氨酶水平. 赵红燕等[36]将60例门诊和住院NAFLD患者随机分成常规治疗组和联合治疗组. 联合治疗组在常规治疗用药基础上, 给予枯草杆菌肠球菌二联活菌胶囊口服. 联合治疗组患者血清TNF-α、IR水平均下降, NAFLD肝内脂肪沉积状况改善. 赵严等[37]指出, 双歧三联活菌(培菲康)可减少NAFLD患者的TNF-α、内毒素血症, 改善肝功能. 马丽滨等[38]选取患者88例, 随机分为对照组及观察组, 对照组予生活方式调整, 观察组使用双歧杆菌三联活菌胶囊8 wk, 两组治疗后ALT及γ-谷氨酰转肽酶(γ-glutamyl transpeptidase, GGT)较观察组下降较明显, 二者差距有统计学意义.

3.2 益生元 益生元是一类能够选择性地促进一种或多种有益菌生长的非消化性低聚糖, 包括乳果糖、乳梨醇、果聚糖、菊糖等制剂. 益生元通过选择性地促进有益菌的生长并提高其定植抗力, 籍以抑制潜在致病菌的生长及其有害代谢物的产生, 从而减少肠源性内毒素血症及其相关损伤. 此外, 乳果糖还可直接灭活内毒素[39], 并通过其酸性代谢产物促进肠蠕动, 从而加快肠道细菌及毒素的排出. Cani等[17]发现给予肥胖小鼠果聚糖灌胃后, 肥胖小鼠盲肠内乳酸杆菌和双歧杆菌等有益菌的数量显著增加, 伴血清内毒素量减少以及肝脏炎性因子和氧化应激标志物的表达下降. 有前瞻性研究指出[40]果糖可显著降低小鼠血清ALT水平, 减轻胰岛素抵抗.

3.3 合生元 合生元是有选择性地将益生菌和益生元组合使用的复合制剂, 旨在起到协同调节肠道微生态平衡的作用. Liu等[41]的实验中, 服用合生元30 d就可显著降低肝硬化并轻度肝性

应用要点

在未来的研究中希望通过进一步加强对肠道微生态的认识, 确定一种或几种微生物与NAFLD明确相关, 从而通过干涉相关的微生物来起到对NAFLD的治疗作用, 并能通过更多的随机对照实验明确益生菌在NAFLD中的规范化应用.

同行评价

本文对肠道微生态环境与非酒精性脂肪性肝病关系进行了系统综述, 包括微生态环境对NAFLD发生的影响、NAFLD患者微生态环境的改变以及调节微生态环境对NAFLD治疗的意义三个方面. 综述选题较为新颖, 选题恰当, 论据较充分.

脑病患者的血氨和内毒素水平, 50%的患者肝性脑病好转.

3.4 小檗碱 小檗碱作用于NAFLD的机制尚不甚清晰, 可能有以下几种: (1)小檗碱通过刺激胰岛细胞分泌胰岛素缓解胰岛素抵抗; (2)作用于腺苷酸活化蛋白激酶(AMP-activated protein kinase, AMPK)级联反应. 肝细胞AMPK通路的激活会导致脂肪酸氧化增加, 减轻胰岛素抵抗[42]; (3)可通过调节肠道菌群改善NAFLD. 有研究[43]表明小檗碱能有效抑制葡萄球菌, 链球菌, 沙门氏菌, 克雷伯菌等多种细菌; (4)小檗碱可通过调节紧密连接蛋白作用降低肠道通透性, 提高肠道的屏障功能, 减轻内毒素引起的肝脏炎症及纤维化反应[44]. 曹毅等[45]研究发现, 黄连素灌胃可降低NAFLD小鼠体质量, 改善肝纤维化和坏死. 李晓翠等[46]给高脂饮食造模的大鼠使用小檗碱灌胃4 wk, 盐酸小檗碱组大鼠的脂肪变性和炎症程度较对照组减轻.

3.5 抗生素 早在20世纪80年代, 曾有学者发现空-回肠旁路术后NAFLD可以应用甲硝唑缓解; Membrez等[47]、Fan等[48]通过诺氟沙星和氨苄青霉素喂养小鼠, 发现可以调节肝脏和肠道中与炎症和代谢相关基因的表达, 肝细胞胰岛素抵抗和脂肪变性均有所改善; Henao-Mejia等[49]在试验中应用环丙沙星和甲硝唑抑制小鼠肠道微生物活性, 明显减轻了NAFLD的严重程度.

4 结论

肠道微生态受遗传、环境、病史等多种因素影响, 个体差异较大, 给研究带来了一定的困难. 目前的多项临床及动物研究表明通过对肠道微生态的干预, 可以减轻患者NAFLD的程度, 改善代谢性疾病情况, 但目前仍缺乏随机、双盲、多中心, 大样本的证据. 同时对于所使用的益生菌的菌种, 剂量及用药时间也缺乏相应的规范. 由此可见, 虽然干预肠道菌群治疗代谢性疾病是目前治疗新思路的一种, 但要付诸临床实践仍有许多亟待解决的问题.

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