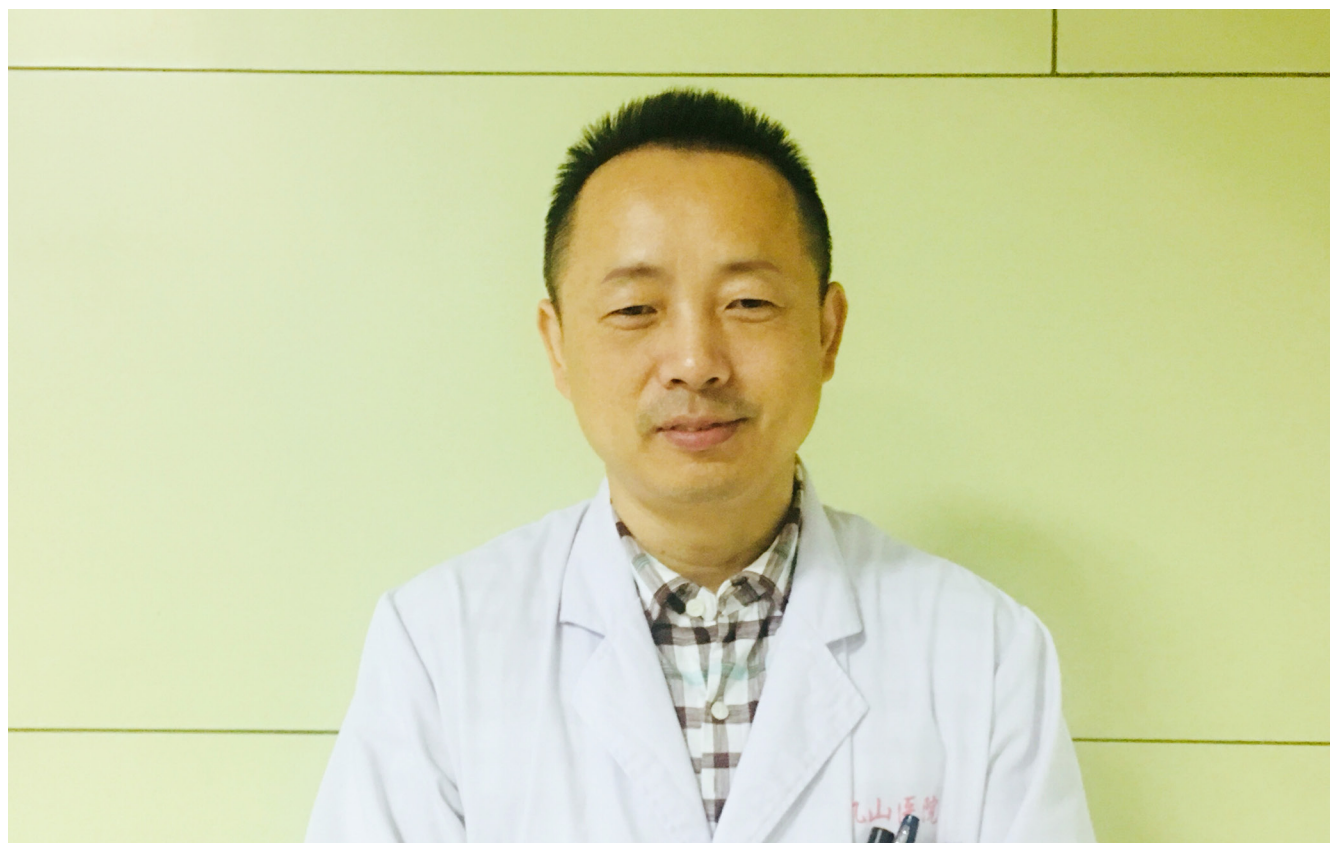


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述评

- 105 湖北“肺炎1号”方治疗新型冠状病毒肺炎的肠道微生态机制探讨
袁榛, 舒兰, 谭周进
- 110 结直肠癌肝转移的外科治疗
吴香安, 石岳, 杜顺达

基础研究

- 116 *CMTM3*在胃癌中的表达及其生物学功能研究
李爱云, 吴玉秀, 郜娜, 张建光, 孟薇

临床研究

- 125 lncRNA HOTAIR在食管鳞癌患者血清中的表达及其意义
达春丽, 刘凯, 孙伟
- 131 思连康联合艾司奥美拉唑钠治疗幽门螺杆菌相关性胃炎疗效及对NF- κ B炎症信号通路的影响
黄龙武, 李雷
- 138 品管圈在肝癌介入手术患者护理中应用效果的Meta分析
楼婷婷

文献综述

- 146 饮食疗法通过肠道菌群治疗溃疡性结肠炎的机制研究进展
刘畅, 吴慧, 范恒

病例报告

- 152 急性A型主动脉夹层并发肠系膜灌注不良综合征1例
柴琳, 王玥, 范阜东, 王东进

消 息

- 109 《世界华人消化杂志》2011年开始不再收取审稿费
124 《世界华人消化杂志》性质、刊登内容及目标
158 《肠道微生物与消化系统疾病》书讯

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Contents

Volume 29 Number 3 February 8, 2021

EDITORIAL

- 105 Mechanism of Hubei "Pneumonia No. 1" decoction for treatment of COVID-19 with regard to intestinal microecology
Yuan Z, Shu L, Tan ZJ
- 110 Surgical treatment of colorectal liver metastasis
Wu XA, Shi Y, Du SD

BASIC RESEARCH

- 116 Expression and biological function of *CMTM3* in gastric cancer
Li AY, Wu YX, Gao N, Zhang JG, Meng W

CLINICAL RESEARCH

- 125 Significance of expression of lncRNA HOTAIR in serum of patients with esophageal squamous cell carcinoma
Da CL, Liu K, Sun W
- 131 Siliankang combined with esomeprazole sodium for treatment of *Helicobacter pylori*-associated gastritis: Efficacy and influence on NF- κ B signaling pathway
Huang LW, Li L
- 138 Meta-analysis of effects of quality control circle activities in nursing care of patients with liver cancer undergoing interventional operation
Lou TT

REVIEW

- 146 Progress in understanding of mechanism of dietary therapy for ulcerative colitis with regard to intestinal microbiota
Liu C, Wu H, Fan H

CASE REPORT

- 152 Acute type A aortic dissection with mesenteric malperfusion syndrome: A case report
Chai L, Wang Y, Fan FD, Wang DJ

Contents

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Volume 29 Number 3 February 8, 2021

COVER

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饮食疗法通过肠道菌群治疗溃疡性结肠炎的机制研究进展

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Progress in understanding of mechanism of dietary therapy for ulcerative colitis with regard to intestinal microbiota

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Abstract

The pathogenesis of ulcerative colitis is closely related to the complex interaction between heredity, environment, and intestinal microbiota. Intestinal dysbiosis is not only the cause of ulcerative colitis, but also the pathological result of ulcerative colitis. Dietary therapies have been found to modulate the microbiota to alter the effects of environmental factors on ulcerative colitis. Dietary pattern is related to the pathogenesis, development, and prognosis of ulcerative colitis, and the role of diet in ulcerative colitis has attracted more and more attention. This article reviews the mechanisms by which dietary therapy treats ulcerative colitis with regard to regulating the brain-gut functional axis, regulating the immune function, and protecting the intestinal mucosal barrier by modulating intestinal microbiota.

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Key Words: Intestinal microbiota; Dietary therapy; Ulcerative colitis

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摘要

溃疡性结肠炎(ulcerative colitis, UC)的发病与遗传、环境和肠道微生物群之间的复杂相互作用密切相关。肠道菌群失调既是溃疡性结肠炎的发病原因, 又是溃疡性结肠炎的病理结果。研究发现, 饮食疗法能调节微生物群以改变环境因素对溃疡性结肠炎的影响。饮

食方式与溃疡性结肠炎的发病、发展及预后整个过程均有关, 在溃疡性结肠炎中的影响也愈渐受到广泛关注. 本文就饮食疗法能通过肠道菌群调节脑-肠功能轴、调节免疫功能、保护肠黏膜屏障来治疗溃疡性结肠炎的机制作一综述.

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关键词: 肠道菌群; 饮食疗法; 溃疡性结肠炎

核心提要: 饮食疗法不仅可以给溃疡性结肠炎(ulcerative colitis, UC)患者提供营养支持, 还能通过调节肠道菌群以调节脑-肠功能轴、保护肠黏膜、调节免疫功能来治疗UC. 饮食疗法因其副作用小, 价格低, 可以长期用于辅助治疗UC, 从而减少对药物的依赖性.

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0 引言

溃疡性结肠炎(ulcerative colitis, UC)作为一种非特异性炎症性疾病, 以腹痛、腹泻、大便夹有黏液脓血为主症, 属于炎症性肠病(inflammatory bowel disease, IBD)的一种. UC的发病率逐年升高, 已演变成一种全球性疾病. 其中, 欧美人群UC发病率高于亚洲人群, 这与西方人低纤维、高蛋白的饮食习惯有关, 且长期患有溃疡性结肠炎人群发生结肠癌类疾病风险更高^[1]. 研究已经证明UC发病与多种因素有关, 如饮食、情绪、免疫失调、肠道菌群失调、遗传因素^[2-5]. 临床多以氨基水杨酸和糖皮质激素、免疫抑制剂、生物制剂来治疗该病, 但易产生依赖性且副作用大. 近年来, 益生菌^[6,7]、饮食疗法^[8]和粪菌移植(fecal microbiota transplantation, FMT)^[9]等干预措施兴起, 用来治疗UC, 临床疗效显著, 副作用小, 其作用的关键机制就在于调节肠道菌群. UC患者经常询问医生需要注意什么饮食禁忌, 往往只得到清淡饮食的回答, 多是由于医师忽视了饮食调养的重要性, 也缺乏相关的营养学专业知识. 而实际上, 饮食疗法可以通过改善肠道菌群来保护肠道健康, 并且可以用于长期缓解肠道炎症, 可与药物配合治疗UC.

1 饮食疗法的分类

饮食疗法, 又称食疗, 即利用食物来影响机体各方面的功能. 《本草纲目》中讲“药食同源”. 由于UC的治疗方法在不同程度上都对药物有一定的依赖性, 因此长期应用有一定的副作用且费用高昂. 而饮食作为人类摄取

营养的必须途径, 不会产生毒副作用, 是可以长期用于调理疾病的. 临床发现改变饮食可以改善UC患者肠道症状, 减轻局部炎症反应, 同时也增强了自身的营养.

UC的饮食疗法目前主要分为排除饮食(elimination diet, ED)和食用膳食补充剂^[10]. 排除饮食是指去除UC患者日常饮食中某些可能诱发或加重消化道症状的食物, 包括特定碳水化合物饮食(specific carbohydrates diet, SCD)、植物性饮食(plant based diet, PBD)、低发酵的低聚糖、双糖、单糖和多元醇饮食(low fermentable oligosaccharides disaccharides monosaccharides and polyols, low FODMAPs)、全胃肠外营养(total parenteral nutrition, TPN), 部分肠外营养(partial parenteral nutrition, PPN)等.

研究最多的一种排除饮食是SCD, 它是一种严格的饮食, 这种饮食包括未加工的肉类、禽类、鸡蛋、鱼类、水果、蔬菜、所有脂肪和油、甜味剂(仅蜂蜜和自制的发酵酸奶)^[11]. 另一种被研究的较多的是半素食饮食(semi-vegetarian diet, SVD), SVD作为PBD的一种, 也就是乳蛋素食, 即每周吃一次鱼, 每两周吃一次肉, 这对UC患者症状起到明显的改善作用^[12]. 其次, 低FODMAPs饮食, 即限制摄入难吸收的短链碳水化合物的饮食方式, 也常被用于治疗UC.

2 饮食疗法在溃疡性结肠中的作用

2.1 营养支持 饮食疗法作为一种膳食规划方法, 最直接的作用就是补充人体所需的营养. UC患者因为UC本身的症状如反复便血、腹泻等导致体内营养流失, 又可能因腹痛、恶心等导致食欲下降. 因此, 营养不良也是UC常见的并发症. 而与此同时, UC患者又因为饮食的限制, 不敢随意补充蛋白含量过高或脂肪过高的膳食. 因此, 有必要推广饮食疗法以指导患者正确合理地补充营养.

长期则应在营养师的监督下进行, 通过营养风险筛查(nutritional risk screening, NRS)进行详细的营养评估和干预, 以避免微量营养素缺乏或营养不良的风险^[13]. 营养状况受损和肠道炎症相互影响可能形成恶性循环. 此外, 营养不良会影响微生物群的组成和活动, 因此也可能影响疾病的病程. UC患者应多食用水果和蔬菜, 并提供抗炎化合物, 如维生素(vitamin, Vit)B3、VitB6、VitE、VitC、胡萝卜素以及锌和镁等^[14]. 高消费肉类或鱼类被怀疑是UC的危险因素, 但鸡蛋或乳制品却不会明显诱发UC^[15]. 因此, 适度的动物蛋白是允许的, 但更建议还是从豆类中提取植物蛋白. 临床有必要制定相关饮食指南, 类似糖尿病膳食指导糖尿病患者一样, 使UC患者可以长期调理自身的营养及肠道健康状况.

2.2 调节肠道菌群的组成及代谢功能 饮食疗法, 不仅能供给人体所必需的营养素, 而且能够调整肠道菌群. 许

多患者因不良饮食习惯使得肠道菌群失调, 导致UC复发. 高纤维饮食能保护肠黏膜.

一项关于饮食对微生物组影响的对照研究表明, 与低脂/高纤维饮食相比, 膳食脂肪的增加和膳食纤维的减少显著改变了肠道微生物群的组成^[16]. 相比之下, 高蛋白和高脂肪会通过饮食诱导肠道微生物群的变化, 导致类杆菌的增多, 增加肠道通透性, 还会加重结肠炎^[17]. 西方饮食的结构中, 纤维摄入量的下降导致能够发酵膳食纤维的微生物数量随之下降. 如研究发现^[18-20], 低纤维饮食会使肠道中拟杆菌、普氏菌、以及双歧杆菌减少; 高碳水化合物、低脂肪饮食导致粪便双歧杆菌、拟杆菌数量显著增加; 而高碳水化合物和低血糖饮食则会促进普拉梭菌粪杆菌的生长. 短链脂肪酸(short-chain fatty acid, SCFAs)作为肠道菌群发酵膳食纤维的产物, 能通过改变基因表达、细胞分化、趋化、增殖和凋亡来调节上皮细胞或免疫细胞的功能^[21]. SCFAs的合成量, 尤其是在结肠中的合成量, 已被作为微生物群健康的间接测量指标. 而高脂饮食却增加了SCFAs的排泄, 降低肠道菌群的多样性^[22].

因此, 食物可能会明显地调节微生物—肠道轴, 在调节微生物群组成和功能方面起着关键作用, 甚至可能影响表观遗传的变化. 如限制饮食中的蛋氨酸可以改善高脂喂养小鼠的肠道菌群, 降低肠道通透性和炎症反应^[23]. 牛乳低聚糖能降低膳食诱导的肥胖小鼠肠道通透性, 改善炎症和微生物异常^[24]. 可溶性膳食纤维的补充, 使得益生菌相对丰度的增加, 能改善肠道炎症反应和减轻肠黏膜损伤^[25].

2.3 减轻炎症反应 临床和实验室都发现了SCD饮食能有效减轻UC患者的炎症反应, 这在儿童和成人UC患者中都有报道^[26,27], 还被证明导致微生物组成的显著变化. 一些患者在SCD试验期结束时至少可以停用一种抗IBD药物. Cox等^[28]研究发现, 低FODMAPs饮食组UC患者与正常饮食组的UC患者相比, 4 wk后, 前者肠道症状明显缓解, 炎症严重程度评分大大下降, 短期来说, 可以帮助控制炎症. 患者应在最初的4-6 wk严格遵守低FODMAPs饮食^[29]. Vidal-Lletjós等^[30]发现在动物模型中, 适度高蛋白剂量可调节黏膜愈合, 非常高蛋白饮食则显示了对这一过程的有害作用. 因此, 总体而言, 特定碳水、适度高蛋白、高纤维等饮食习惯适用于治疗UC, 具有强烈的抗炎特性, 并显示出改善疾病症状的可能.

而膳食补充剂也对UC有着较好的效果, 如服用维生素D和姜黄素可以减轻UC患者的肠道炎症症状^[31,32]. 另外, 饮食中的鱼油或亚麻油, 已经用于抗炎治疗. Scaiola等^[33]报道多不饱和脂肪酸可能具有抗炎活性, 能够减少炎症介质含量, 抑制UC的免疫反应和炎症过程.

2.4 影响UC的发病和预后 UC的流行病学研究发现摄入过多脂肪或不饱和脂肪酸、高蔗糖等可能会损伤结肠黏膜而增加患病率, 而摄入低脂、高纤维的人患UC的风险会减少^[34]. 饮食中的某些含硫化合物也会对结肠细胞产生一定的直接毒性作用, 比如西方饮食(总体上较高的卡路里摄入量, 尤其是动物蛋白质、糖、精制碳水化合物和超加工食品)可能通过抑制丁酸盐的氧化而对结肠细胞产生负面影响, 与UC发病呈正相关. 另外, 低脂、高纤维饮食能够促进肠道自身愈合^[35]. 因此通过饮食疗法则可以在一定程度上保护肠黏膜、调节肠道菌群而减少UC的发病和复发几率.

3 饮食疗法调节肠道菌群在UC中的作用机制

肠道菌群是人体肠道的正常微生物, 能合成多种人体生长发育必需的物质. 肠道菌群分为有益菌(如双歧杆菌、乳杆菌、普氏菌)、条件致病菌(如肠球菌、肠杆菌)、病原菌(如变形杆菌、金黄色葡萄球菌)三种. UC活动期患者肠道菌群明显不同于健康人, 厌氧菌(如双歧杆菌、拟杆菌、乳酸杆菌)明显减少, 需氧菌(如肠球菌、链球菌)总数升高^[36,37]. 与健康个体相比, 溃疡性结肠炎患者的粪便微生物群中拟杆菌门和厚壁菌门的比例也显著降低. 因此, 一些优势共生体成员(如IV型梭状芽孢杆菌)的丰度减少, 以及有害细菌(如硫酸盐还原菌和大肠杆菌)的增加是UC发病的机制之一^[38]. 而饮食疗法可以调节肠道菌群, 增加有益菌的数量和丰度, 从而达到治疗UC的目的.

3.1 介导脑—肠功能轴 临床发现, UC患者的生活质量不佳, 且压力和抑郁会增加复发几率. 心理应激可能通过改变脑—肠轴功能影响溃疡性结肠炎发病^[39,40]. 许多UC患者伴随着抑郁状态, 严重影响生活质量, 而经抗抑郁治疗后, 患者的抑郁系数明显下降且肠道炎症显著减轻. 通过调节UC小鼠的抑郁状态, 也发现肠道菌群的丰度增加. 一方面, 情绪会影响胃肠道动力; 另一方面, 肠道菌群的变化反过来导致细菌产生各种物质, 刺激肠神经系统和迷走神经传入, 并促进HPA轴的额外激活^[41].

富含益生菌的饮食对肠道和大脑之间的双向联系非常重要^[42]. 肠道和大脑之间的相互作用通过各种细菌的代谢物如SCFAs和它们穿越血脑屏障的能力以及具有神经活性的特性, 增加肠道通透性^[43]. 而饮食疗法通过改变肠道菌群, 能参与调节肠—脑轴, 对UC患者的心理状态和肠道炎症反应起到积极的治疗作用^[44,45].

3.2 调节免疫作用 UC的发展最终可归结于免疫异常, 肠道炎症主要是由巨噬细胞导致的. 促炎因子主要有白介素(interleukin, IL)-6、IL-8、IL-22等, 抑炎因子有IL-10、IL-2、转化生长因子-β(transforming growth factor beta,

TGF- β)等。UC活动期, 促炎因子明显升高^[46]。肠道菌群显示出重要的代谢和免疫功能, 除了参与胆汁代谢, 还分解产生SCFAs, 促进免疫调节。如乳酸能刺激共生肠道细菌的生长, 提高SCFAs水平(特别是丁酸盐), 丁酸盐浓度的增加对炎症反应和伤口愈合时间有正向影响^[47]。研究证明饮食中的丁酸盐通过抑制JAK2/STAT3通路、改善菌群的代谢紊乱, 从而降低炎症因子、减轻炎症反应; 还能抑制组蛋白脱乙酰酶(histone deacetylase, HDAC)活动, 通过自噬途径的激活抑制NF- κ B的作用^[48,49]。

因此, 细菌代谢物介导共生菌群和免疫系统之间的沟通, 影响促炎和抗炎机制之间的平衡。饮食一方面本身即可以释放抑炎因子, 如 ω -3多不饱和脂肪酸(深海鱼类内脏中富含该脂肪酸), 还能下调炎症因子、抑制巨噬细胞中NF- κ B活化, 降低调节性T细胞增殖水平^[50]。另一方面可以调节肠道菌群, 使其产生丰富的SCFAs, 以调节先天和适应性免疫应答。

3.3 保护肠黏膜屏障 肠黏膜是保护大肠受损的第一道屏障, 肠黏膜障碍在UC发病机制中占有重要地位。肠黏膜屏障分为免疫、机械、生物、化学屏障等4个部分。肠黏膜屏障不是静态的屏障, 而是与肠道微生物群和机体细胞发生强烈的相互作用。而稳定的微生物群和黏液层对于防止病原菌引起宿主感染是必不可少的。

肠道微生物群通过影响肠道免疫系统, 如调节Th17/Treg平衡等, 从而阻止病原微生物定植于肠上皮细胞^[51], 保护免疫屏障。机械屏障(即肠道表面覆盖的黏液层)主要由肠道上皮细胞和紧密连接复合体构成。紧密连接复合体, 它由密封蛋白(Claudins)、紧密连接咬合蛋白(Occludins)、闭锁小带(zonula occludens-1, ZO-1)和连接粘附分子组成。如双歧杆菌可以增加ZO-1、Occludins的表达^[52], 口服鼠李糖乳杆菌和普拉梭菌通过增加小鼠结肠上皮细胞Occludins和E-钙黏蛋白(E-cadherin)的水平^[53], 能恢复上皮通透性的缺陷。肠道菌群作为微生物群体, 也可以直接保护生物屏障, 对维持上皮通透性和完整性有深远的影响。另外, 肠道菌群分解产生的SCFAs作为上皮细胞和杯状细胞增殖的直接能量来源, 也能促进肠黏膜屏障的修复。此外, 许多研究证明饮食不仅可以调节肠道菌群, 还对化学屏障、机械屏障有不同程度的影响^[54,55]。膳食添加化合物, 如谷氨酰胺也可降低肠道通透性, 改善肠道屏障功能。

4 结论

饮食疗法在维持肠道健康方面发挥着重要的作用, 贯穿UC的发病、发展及预后的全过程。它不仅可以给UC患者提供营养支持, 还能通过微生物群影响肠道黏膜屏障。更重要是能通过调节肠道菌群的配置、产生丰富的

SCFAs, 以调节免疫功能和微生物-脑-肠轴功能, 改善UC患者的情绪及肠道状态。肠道菌群与宿主免疫系统相互作用, 抑制病理生物的扩张, 促进饮食底物的消化, 同时与宿主免疫系统保持联系和调节。富含纤维的饮食有利于能够分解纤维素和木聚糖水解释的细菌生存, 可以保护宿主免受炎症和非感染性结肠疾病的伤害^[56]。因此, 经饮食疗法调节后的肠道菌群的稳态对UC症状具有明显的缓解作用。不同类型的功能膳食成分, 如膳食纤维、益生菌和多不饱和脂肪酸等都对肠道健康有着积极的影响。因此, 根据肠道菌群的特性, 我们可以通过饮食、服用益生菌、粪菌移植来恢复肠道菌群的平衡。所以, UC患者推荐采用高纤维、低精糖或加工食品的平衡植物性饮食。总之, 有必要将饮食疗法作为治疗UC的重要手段之一。

然而, 饮食疗法直接作用于UC的机制尚不明确, 所以在饮食疗法广泛用于UC患者之前, 需要进行大型临床试验、高质量的饮食干预研究来确定治疗成功的膳食成分, 并且结合营养学专家意见, 以促进为UC患者制定循证饮食指南。

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