·综 述·

肠道菌群在血液透析患者心血管疾病中作用及靶向干预研究进展

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摘要：血液透析是终末期肾病患者的重要治疗方法之一。尿毒症状态、饮食习惯、药物使用及透析治疗本身均可能改变肠道生化环境，导致肠道菌群失衡和血清尿毒症毒素蓄积。肠道菌群代谢产物硫酸吲哚酚和硫酸对甲酚是重要的肠源性尿毒症毒素，这两种物质具有较高的蛋白结合力，使其难以通过传统透析有效清除，在血清中蓄积，从而增加心血管事件风险。本文就血液透析患者肠道菌群及其代谢物变化、与心血管疾病的相关性、以肠道菌群为靶点的干预措施的研究进展作一综述。

关键词：肠道菌群；心血管疾病；血液透析

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Role and targeted intervention of gut microbiota in cardiovascular disease in hemodialysis patients

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Abstract: Hemodialysis is one of the most important treatments for patients with end-stage renal disease. The uremic state, dietary habits, drug use, and dialysis treatment itself may alter the biochemical environment of the gut, which often leads to gut microbiota imbalance and serum uremic toxins accumulation. Indoxyl sulfate and p-cresyl sulfate, the metabolites of gut microbiota, are important gut-derived uremic toxins. These two substances have a high protein-binding capacity and accumulate in serum since they are difficult to be effectively removed by traditional dialysis, which increase the risk of cardiovascular events. This paper reviews the research progress of the changes of gut microbiota and its metabolites in hemodialysis patients, the correlation between gut microbiota and cardiovascular disease, and the intervention measures targeting gut microbiota.

Keywords: gut microbiota; cardiovascular disease; hemodialysis

随着慢性肾脏病发病率的持续增长，行血液透析(hemodialysis, HD)治疗患者也逐年增加。根据全国血液净化登记系统最新数据显示，截至 2023 年末，全国登记的 HD 患者总数已达 91.6 万人。HD 可部分替代肾脏功能，清除血液中小分子代谢废物或有害物质，如肌酐、尿素氮、体内多余水分和其他小分子毒素，

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以减少容积负荷并维持电解质和酸碱平衡。但由于HD患者发生多种复杂病理生理变化(如代谢紊乱、免疫系统异常等),导致其肠道菌群的组成与健康人群存在明显差异。此外,透析导管干预、透析患者饮食限制(水果蔬菜摄入不足)及透析相关并发症均可破坏肠道微环境,导致肠道菌群组成改变[1-2]。肠道菌群代谢产物如硫酸对甲酚(p-cresyl sulfate, pCS)、硫酸吲哚酚(indoxyl sulfate, IS)是目前研究最多的肠源性尿毒症毒素,可诱发全身微炎症状态,增大心血管疾病的风险[3]。心血管疾病是HD人群死亡的主要原因,而肠道菌群是心血管疾病中关键的调节因素及潜在的治疗靶点。通过改变肠道菌群的组成结构或调节其代谢产物的水平,有可能为心血管疾病的预防和治疗提供新思路。本文就HD患者肠道菌群及其代谢物变化、与心血管疾病的相关性、以肠道菌群为靶点的干预措施的研究进展综述如下。

1 HD患者肠道菌群特征

1978年Simenhoff等[4]比较15例尿毒症患者和盲袢综合征患者的小肠细菌菌群情况,发现尿毒症患者十二指肠和空肠部位的厌氧菌及需氧菌数量增多。与健康受试者相比,透析前终末期肾病患者颤螺菌属和布劳特氏菌属相对丰度明显增高,SMB53相对丰度降低[5]。Vaziri等[1]报道,行HD治疗后的终末期肾病患者放线菌门、厚壁菌门(尤其是梭菌亚门)和变形菌门(主要是伽玛变形菌纲)相对丰度明显增高。Stadlbauer等[6]发现HD患者潜在致病菌卵形布劳特氏菌、奇特龙梭菌和鲍氏梭菌增多,有益微生物种类减少。有研究[7]在儿童HD患者中观察到拟杆菌门增多。但HD人群肠道菌群变化的原因是由于透析本身导致还是肾衰竭本身导致尚不清楚。Luo等[5]研究发现,与透析前终末期肾病患者比较,HD患者普雷沃氏菌属和副普雷沃氏菌属相对丰度明显降低,而阿克曼氏菌属、粪球菌属、不动杆菌属、变形菌属和假单胞菌属丰度明显增高。上述研究表明HD患者存在肠道菌群紊乱,表现为恢复了部分有益菌相对丰度,但诱发了一些潜在的致病菌。

2 HD患者肠道菌群与心血管疾病的关系

循环微生物组在心血管疾病的发病机制中发挥重要作用。肠道菌群组成改变被认为是肠道屏障破坏和炎症的驱动力,导致患者心血管疾病风险增大。在门水平上,菌群失调(尤其是血液变形菌门比例增高)可预测普通人群心血管事件的长期预后[8]。与健康个体相比,心血管疾病患者血液中变形菌门丰度明显增高,而厚壁菌门丰度明显降低[9]。有研究[10]表明,变形菌门水平升高与心血管事件有关。变形菌门的外膜由脂多糖组成,可导致内毒素血症、免疫系统激活和炎症,这些均是心血管疾病发生、发展的关键因素[11]。但以上这些研究排除了肾病患者,尤其是已进入透析阶段的患者,该类患者早期心血管疾病发病率和病死率均较高[12]。研究[13]发现,排除年龄、性别、种族、透析时间及血管通路类型等混杂因素后,HD患者血液中放线菌门比例较高、变形菌门比例较低仍与心血管疾病病死率高独立相关。该研究结果与普通人群和心血管疾病患者中观察到的变形菌门水平升高与心血管事件有关相矛盾。造成这种差异的原因有多种:首先,研究对象不同可能导致结果的差异,HD患者由于肾脏功能丧失,体内代谢废物积累和清除机制发生变化,有可能影响血液中微生物组成;其次,用于评估循环微生物特征的血液样本处理方式可能存在差异,如采样时间、样本保存条件及实验室检测方法不同均可能影响最终结果;此外,HD患者常伴有多种并发症,如高血压、糖尿病等,这些因素也可能对微生物群落产生影响。因此,在解释HD患者微生物群变化时需综合考虑多种因素的相互作用。在属水平,因心血管疾病死亡的终末期肾病患者产生短链脂肪酸的拟杆菌属和考拉杆菌属减少[5]。拟杆菌属可有效降低胆固醇水平、预防肥胖并降低心血管疾病的患病风险[14]。拟杆菌属可通过减少脂多糖产生,发挥有效预防动脉粥样硬化的作用[15]。

肠道菌群也可通过代谢产物如IS和pCS参与心血管疾病的发生、发展。IS是色氨酸代谢产物,色氨酸经大肠埃希菌分解产生吲哚,吲哚经结肠吸收后在肝脏中进一步被氧化和硫酸化形成IS[16]。pCS是酪氨酸和苯丙氨酸代谢产物,在结肠细菌的脱氨、转氨和脱羧反应下,酪氨酸和苯丙氨酸转化为苯酚和对甲酚,然后进一步在结肠黏膜和肝脏中被硫酸化为小分子物质pCS[16]。在循环中IS和pCS与白蛋白紧密结合在一起,结合率高达90%以上,在肾功能正常情况下通过尿液排出体外[17]。HD患者血浆游离IS和pCS水平明显升高,是肾功能受损、肠道菌群失调、代谢异常等多种因素共同作用的结果,且由于IS和pCS高蛋白质结合性质,传统透析无法达到由肾小管分泌实现的高清除率[18]。此外,HD患者由于水果和蔬菜摄入受限、服用磷酸盐结合剂或钾吸附剂等原因常引起便秘,而结肠转运时间延长将导致肠道中分解蛋白质的菌群数量增多。由于蛋白质在胃肠道停留时间延长,最终导致蛋白结合类尿毒症毒素的含量增高[19]。研究[20]发现,血清IS、pCS水平随肾功能恶化、体内毒素积累而增高,行HD的慢性肾脏病患者血清IS、pCS水平最高。

IS、pCS水平与慢性肾脏病患者和HD患者心血管疾病的发生、发展存在密切联系。Barreto等[21]研究发现,随慢性肾脏病分期的进展,血清IS水平逐渐升高,与主动脉钙化、血管僵硬度增高呈正相关。血清

IS 水平是预测晚期慢性肾脏病患者心血管疾病风险的重要指标[22]。有研究[23]对 HD 患者中位随访 48 个月，排除传统心血管风险（如高血压、糖尿病等）及非传统心血管风险（如炎症标志物）等混杂因素后，血浆 IS 水平与 HD 患者首次心力衰竭事件的发生风险仍独立相关。此外，Wu 等[24]研究发现，HD 患者血清 IS 是血管内介入治疗后透析移植物血栓形成的危险因素。游离 pCS 是慢性肾脏病患者总体病死率和心血管病死率的预测因素[25]。HD 患者血清总 pCS 水平与冠心病发病率呈显著正相关[26]。血清 pCS 是老年 HD 患者心血管事件的良好预测指标[27]。以上研究提示 IS 和 pCS 可作为慢性肾脏病和 HD 患者心血管疾病的危险因素，其可通过多种机制影响心血管系统：(1)IS 通过促进氧化应激，直接损害心肌细胞，导致心肌纤维化、心肌肥大及心肌细胞凋亡等多种心脏病变[28]。(2)IS 通过激活 MAPK 信号通路，诱导血管平滑肌细胞增殖，推动动脉硬化进程。(3)IS 还可能通过诱导血管炎症，在动脉粥样硬化的发生中发挥作用；IS 可上调 E-选择素表达，促进白细胞与内皮细胞之间的相互作用，加剧血管壁炎性反应[29]。(4)IS 不仅诱导氧化应激，还通过多种机制对内皮细胞产生负面影响；IS 可抑制一氧化氮生成，导致血管内皮细胞功能受影响[30]。此外，IS 还表现出对人脐静脉内皮细胞增殖和伤口愈合能力的抑制作用[31]。(5)pCS 通过增强血管内皮细胞和平滑肌细胞中活性氧产生，从而导致细胞毒性[32]。(6)pCS 可促进 HD 患者循环中内皮损伤标志物内皮微粒产生，与血管内皮损伤有关[33]。

3 HD 患者肠道菌群的干预措施

3.1 益生菌 益生菌是一种含活性微生物或其成分的制剂，主要被用于调节人体内微生物平衡。HD 患者补充含粪肠球菌、长双歧杆菌和嗜酸乳杆菌的益生菌粉可恢复厚壁菌门水平，抑制结肠中有害细菌过度生长[34]。益生菌可有效减少 HD 患者血清尿毒症毒素前体，如苯酚和对甲酚[35]。益生菌还可有效降低 HD 患者体内炎症标志物，如 C 反应蛋白、白细胞介素-6 等[36-37]。此外，益生菌还可降低 HD 患者氧化应激标志物血浆丙二醛水平，增强机体抗氧化能力[38]。但也有研究[36,39]表明，HD 患者补充益生菌在改善尿毒症毒素、炎症标志物水平上并无明显作用。因此，益生菌对 HD 患者肠道菌群的作用还需进一步研究证实。

3.2 益生元 益生元是指一些不可消化的食物成分，可选择性地促进生物体有益菌的代谢和增殖。研究[40]表明，菊粉可增加 HD 患者疣微菌门及其阿克曼菌属相对丰度，增加粪便中短链脂肪酸浓度。富含低聚果糖的菊粉可降低 HD 患者 pCS 水平[41]。部分水解瓜尔胶是一种可溶性膳食纤维，摄入含部分水解瓜尔胶的益生元可调节肠道菌群失调[42]。一种天然食品色素姜黄素是一种亲脂性酚类益生元，可减少 HD 患者 pCS 产生，具有抗炎和抗氧化特性[43-44]。抗性淀粉是不被小肠酶解的淀粉和淀粉降解产物的总称，在玉米和土豆中含量丰富，抗性淀粉可抵抗小肠中胰腺 α-淀粉酶酶解，到达大肠通过细菌发酵产生的短链脂肪酸发挥有益作用[45]。丁酸盐等短链脂肪酸有较强抗炎特性，可通过抑制活化的核因子-κB 细胞信号通路，减少炎性因子和趋化因子产生[46]。研究[47-48]发现，补充抗性淀粉可降低 HD 患者白细胞介素-6 和 IS 水平，下调核因子-κB mRNA 表达。抗性淀粉 2 型可有效增加产短链脂肪酸类菌群，如罗斯拜瑞氏菌属和高氏瘤胃球菌[49]。

3.3 合生元 合生元是益生元和益生菌的复合制剂。有研究[50]对 58 例 HD 患者补充合生元 7 周后，结果发现 HD 患者结肠 pH 及血清 pCS、IS 水平降低。补充合生元可增加双歧杆菌数量，有利于维持肠道菌群稳态[51]。此外，HD 患者摄入合生元可明显改善便秘，提高生活质量[52]。

3.4 AST-120 AST-120 是一种口服的球形活性炭，由直径为 0.2～0.4 mm 的多孔碳颗粒组成，不溶于水和常见有机溶剂，其可吸附酸性和碱性有机化合物，尤其是小分子尿毒症毒素[53]。有研究[54]发现，AST-120 可降低慢性肾脏病患者血清 IS 水平，推迟肾透析时间，HD 患者进行 2 周 AST-120 治疗后，IS、pCS 水平均降低，内皮功能障碍明显改善。IS 通过产生氧化应激抑制内皮细胞增殖和修复，诱导内皮细胞功能受损，而内皮功能障碍是 HD 患者发生心血管疾病的重要因素。

3.5 粪便微生物移植（fecal microbiota transplantation，FMT） FMT 是将健康人肠道微生物群传递给患者，从而恢复肠道菌群功能。但 FMT 在 HD 患者中应用的报道较少，仅有关于 FMT 在慢性肾脏病患者中应用的个案报道。1 例膜性肾病患者行 FMT 治疗 2 次后，腹泻症状明显缓解，肾功能指标明显改善[55]。2 例 IgA 肾病患者行 FMT 治疗 6～7 个月，肠道生态失调和肾功能均明显改善[56]。但有研究[57]对艰难梭菌感染的不同 FMT 治疗方案进行评估，结果发现 HD 患者失败比例高于其他治疗者，表明 HD 可能影响 FMT 的疗效。

4 结 语

HD 患者生理病理变化可影响肠道微生物群落。肠道细菌来源的毒素通过 HD 患者受损的肠上皮屏障进入血液，对心血管系统造成损伤。目前旨在调节肠道菌群失调和清除循环肠源性尿毒症毒素的干预措施主要集中在膳食补充剂上，益生菌/益生元可恢复肠道微生物组成、减少尿毒症毒素、减少炎症和氧化应激标

志物等，为HD患者心血管疾病的临床预防和治疗提供了新思路。但目前研究缺乏针对心血管事件发生率、病死率等方面的干预性研究，未来还需进一步研究分析HD患者微生物多样性与心血管疾病的复杂关系。

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