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Hans汉斯

基于肠道微生态治疗糖尿病肾病的研究进展

纪新建[1]，张志芳[2*]，祁　乐[1]，刘雅倩[1]，闫鑫媛[1]，张欣雨[1]，陈明昊[1]

[1]内蒙古医科大学中医学院，内蒙古　呼和浩特
[2]内蒙古医科大学方剂学教研室，内蒙古　呼和浩特

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摘　要

肠道微生态在糖尿病肾病(DKD)进展中的作用越来越受到关注。一方面，肾功能下降会增加循环尿毒症毒素，影响肠道菌群的组成和功能。另一方面，肠道菌群失调会破坏上皮屏障，导致内毒素暴露增加，诱发微生态炎症级联反应，包括抑制黏附分子、趋化因子、细胞因子、免疫细胞和细胞内信号通路的表达，从而加剧肾脏损伤。本综述主要总结了肠－肾轴在糖尿病肾病进展中的证据，以期为糖尿病肾病的临床治疗提供新的思路。

关键词

肠道菌群，肠肾轴，糖尿病肾病

Research Progress in the Treatment of Diabetic Nephropathy Based on Intestinal Microecology

Xinjian Ji[1], Zhifang Zhang[2*], Le Qi[1], Yaqian Liu[1], Xinyuan Yan[1], Xinyu Zhang[1], Minghao Chen[1]

[1]College of Traditional Chinese Medicine, Inner Mongolia Medical University, Hohhot Inner Mongolia
[2]Prescription Science Teaching and Research Section of Inner Mongolia Medical University, Hohhot Inner Mongolia

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Abstract

The role of intestinal microecology in the progression of diabetic nephropathy (DKD) has attracted more and more attention. On the one hand, decreased renal function will increase circu-

*通讯作者。

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lating uremic toxins and affect the composition and function of intestinal flora. On the other hand, the imbalance of intestinal flora can destroy the epithelial barrier, lead to increased endotoxin exposure, and induce microecological inflammatory cascade reactions, including inhibition of the expression of adhesion molecules, chemokines, cytokines, immune cells and intracellular signal pathways, thus aggravating renal damage. This review mainly summarizes the evidence of enterorenal axis in the progression of diabetic nephropathy, in order to provide new ideas for the clinical treatment of diabetic nephropathy.

Keywords

Intestinal Flora, Enterorenal Axis, Diabetic Nephropathy

1. 引言

人体拥有数量众多的微生物群，尤其胃肠道中菌群基因编码数量是人类基因总量 150 倍，被认为是人类“第二个”基因组。这些微生物组调节人类基因组的相互作用影响人体的生理代谢，并发挥结构和组织学功能[1]。人体内环境代谢、免疫、内分泌等主要功能与肠道菌群有密切联系[2]。在正常情况下，肠道菌群相对稳定，在肠道中保持共生和拮抗关系。当肠道菌群的组成发生变化时，在营养状况、病态等因素发生变化的情况下，微生物群的平衡被打破，即细菌群落的生态失调[3] [4]。肠道菌群失调可影响胰岛素抵抗(IR)、胆汁酸(BA)代谢、炎症反应和肠道通透性增加，这些慢性低度炎症状态被认为是糖尿病及其并发症如糖尿病肾病(diabetic nephropathy, DKD)的标志[5] [6] [7]。因此，维持肠道菌群的多样性和平衡对于调节宿主的健康维持和稳态至关重要。

糖尿病肾病(DKD)是慢性肾脏病(chronic kidkdey disease, CKD)的一种，是糖尿病(diabetes mellitus, DM)的常见并发症之一，是大多数国家和地区导致终末期肾病(end-stage renal disease, ESRD)的主要原因[8]。在过去十年中，中国 DKD 发病率和患病率显著上升，估计 DKD 人口为 2430 万。值得注意的是，1 型糖尿病(T1D)和 2 型糖尿病(T2D)均在一定程度上发生 DKD，其中 T1D 出现的可能性更大，但由于临床上 T2D 患者基数更多，导致由 T2D 发展成的 DKD 患者人数占比更多[9]。DKD 的临床症状为蛋白尿增加、GFR 进行性降低、持续性肾小管损伤或内皮微血管损伤。然而，DKD 的机制尚未完全阐明[10]。尽管传统的治疗方法以细致的血糖和血压调节为重点，DKD 不可避免地向相关死亡率较高如终末期肾病(ESRD)的发展仍然没有减少[11]。这种现象不仅可以归因于受扰的葡萄糖代谢和活性氧物种(ROS)的产生，还可以归因于慢性低度炎症的潜在状态[12]。调节肠道菌群失调导致的微生态炎症级联反应，包括抑制黏附分子、趋化因子、细胞因子、免疫细胞和细胞内信号通路，具有关键意义[7]。相关系列报道表明，DKD 患者肠道中菌群大量死亡，来自细菌死亡时脱落的内毒素 LPS 可被 toll 样受体-4 识别，并通过 MyD88 触发信号转导，激活 NF-κB 和丝裂原活化蛋白激酶，从而促进肾脏炎症[13]。除了上述和目前已知的分子信号传导外，微生物群衍生的代谢物，如短链脂肪酸(SCFAs)、次级胆汁酸(BAs)和其他尿毒症毒素也可能参与其中[14]。

因此，为了阐明 DKD 的发病机制，我们将首先总结肠肾轴理论，包括 DKD 进展中肾屏障和肠道通透性以及肠道菌群组成的变化。然后，将讨论微生物群衍生代谢物(如 SCFAs、LPS 和尿毒症毒素)对 DKD

进展的影响。

2. 肠－肾轴

在过去几年中，人们提出了肠道和肾脏之间的密切联系，称为肠－肾轴，强调双向交互作用[15]。肾损伤与尿毒症毒素在肠道中的积聚和肠道通透性增加有关。DKD 患者胃肠道中尿素含量高于正常水平，含尿素酶的细菌可将其转化为氢氧化氨，从而升高肠腔 pH 值，导致与肠屏障功能密切相关的肠细胞紧密连接蛋白 ZO-1 丢失和黏液蛋白 MUC2 产生减少造成肠黏膜破坏，加重全身炎症反应及肾脏损伤[16] [17]。另一方面，DKD 患者后期肾功能严重损害，许多含氮产物通过肠道释放可能导致肠道病原体大量增殖，加重肠道菌群的紊乱[18]。

同时，菌群失调和肠道屏障功能受损也可能通过微生物群的内毒素和代谢产物诱发全身炎症，导致肾功能恶化[19]。在肾脏疾病患者中，携带对甲酚和吲哚形成酶的肠道细菌过度生长，并促进酪氨酸和色氨酸的发酵，从而增加循环中尿毒症毒素如吲哚酚硫酸盐、对甲酚和对甲酚硫酸盐的水平[20]。这些尿毒症毒素通过 OATs 进入肾小管细胞，它们可以刺激 TGF-β1、趋化因子和氧化自由基的产生，在肾小管和肾小球室中诱导氧化应激和炎症，导致肾脏间质纤维化和硬化。肠道通透性增加可能导致脂多糖(lipopolysaccharide, LPS)持续浸润到门静脉，导致代谢性内毒素血症和炎性细胞因子水平升高，从而加速 DKD 的进展[21]。LPS 是革兰氏阴性菌的表面抗原，通过 TLR2 和 TLR4 相关通路介导宿主炎症[22]。研究表明，TLR2 和 TLR4 通过诱导肿瘤坏死因子——α (TNF-α)、白细胞介素-1 (IL-1)和 IL-6 等促炎细胞因子的释放，以及核因子-κB (NF-κB)介导的炎症级联反应的激活，参与 DKD 的持续炎症反应过程[23]。

综上所述，胃肠道和肾脏双方的变化会通过肠黏膜、菌群、免疫炎症等方面影响另一方，导致不良后果。

3. DKD 患者肠道微生态变化

1、DKD 的肠黏膜屏障通透性变化

胃肠道是人体连接内部和外部环境的主要纽带，是营养物质和药物通过渗透的限制障碍。因此，其屏障的完整性至关重要。

紧密连接蛋白(Recombinant Tight Junction Protein, TJP)连接吸收肠细胞并分离其顶端和基底外侧膜。TJP 蛋白通过调控细胞旁途径[24] [25]、营养吸收、废物清除[26]、肠道稳态[27]和防御病原体入侵来调节上皮通透性[28]。TJP 蛋白由四种跨膜蛋白(如闭塞蛋白(occluding, OCLN)、claudins (claudins, CLDKD))和支架蛋白如闭合带蛋白-1 (zonula occludens-1, ZO-1)和闭合带蛋白-2 (zonula occludens-2, ZO-2)组成，它们结合跨膜蛋白并将其与细胞骨架肌动蛋白连接[29]。TJP 复合蛋白是动态结构，由包括细菌和细菌产物在内的刺激而发生突变[30]。各种研究表明，肠道通透性紊乱与 TJP 的表达和易位降低有关。因此，肠道屏障 TJP 结构缺陷可能是以肠肾轴为支点的 DKD 患者肾脏进一步损伤的关键因素之一[24] [31]。

DKD 患者肠道菌群组成和功能的改变导致肠上皮屏障受损，肠道通透性增加[32]。具体而言，由于 DKD 患者肾滤过率降低，大量尿素水解导致氨的重吸收增加，随后尿素在肝脏中重新合成，导致跨上皮电阻(transepithelial electrical resistance, TER)显著降低，并导致关键的紧密连接蛋白丢失，如 claudin-1、occludin 和 zonula occludens-1 (zonula occludens-1, ZO-1) [16]。氨还可转化为氢氧化氨，从而引起肠道 pH 值升高，加重肠黏膜损伤，导致上皮屏障结构和功能障碍[17]。此外，肠上皮紧密连接的破坏导致微生物成分进入下面的组织室，引发局部炎症过程，进而导致肠道屏障损伤的持续存在[33]。甲酚、吲哚酚、LPS 和其他毒素随后被转移到血液中，从而诱发全身炎症，进一步促进 DKD 的发病机制[34]。

2、DKD 的肠道菌群失调

人体肠道中有大量的微生物组，主要由拟杆菌门、*厚壁*菌门、*变形*菌门和*放线菌门*组成。肠道微生物组可以调节营养物质的消化和吸收，并为肠上皮细胞提供能量[35]。同时，为了避免肠道微生物组引起的有害免疫反应，宿主和肠道微生物组通过双向交流相互合作进化和适应，并逐渐建立互利关系[36]。人体免疫系统已经开发出一系列进化策略来抑制微生物群，在稳态条件下限制细菌易位和组织炎症，包括黏液、免疫球蛋白 A 的大量产生、调节反应的诱导和抗菌肽的合成[37]。

DKD 患者肠道微生物群处于紊乱状态。如益生菌(如双歧杆菌、乳酸杆菌和普雷沃氏菌)相对丰度的下降以及致病菌(如共原杆菌和去磺酰基杆菌)数量的增加证实了 DKD 与肠道菌群的内在联系[38]。Li 等[39]发现 Allobaculum 和厌氧孢子杆菌会加重 DKD 患者的肾功能恶化，而 Blautia 可能在小鼠中起保护作用。在急性肾损伤 AKI 小鼠中也发现了类似的变化[40] [41]。此外，在肾病患者中也可以检测到与尿毒症毒素相关的微生物群变化，以厌氧革兰氏阳性菌科 Christensenellaceae、Lachnospiraceae 和 Ruminococcaceae 为代表[42]。产丁酸盐细菌 Roseburia 和粪杆菌与患者的肾功能呈负相关[43] [44]。最近的一项研究表明，与健康受试者相比，糖尿病肾病患者的肠道微生物组丰富度降低；具体而言，Coriobacteriaceae 在 DKD 受试者中富集，而 Prevotellaceae 是健康个体中含量最高的细菌。研究人员还发现，通过分析糖尿病患者、DKD 患者和健康对照者之间的微生物差异，Prevotella_9 水平可以准确预测糖尿病患者。与无肾脏并发症的糖尿病患者相比，DKD 患者可以通过大肠杆菌－志贺氏菌和 Prevotella_9 变量准确区分，前者显著升高，后者显著降低[45]。其他研究报告称，肠杆菌科细菌在 DKD 患者中比在健康个体中更丰富[46]。此外，肠杆菌科的相对丰度增加也可能与炎症反应有关，因为它们表达有效的免疫兴奋剂，如 LPS 和肽聚糖(PGN)。

另一方面，DKD 小鼠模型显示厚壁菌门/*拟杆*菌门(F/B)比值下降[39]，*厚壁菌门*水平与 DKD 的肾损伤程度呈负相关，这似乎与目前认为 F/B 比值增加表明健康状况较差的观点相矛盾[47]。健康哺乳动物的 F/B 比值相对稳定，F/B 比值的增加或减少可能代表疾病状态。然而，是否是疾病状态，已经不能仅仅根据 F/B 的比例来判断，需要更多的数据来明确 F/B 的确切作用。尽管动物模型不能充分代表人类的疾病进展，但这些发现为肠道微生物群在糖尿病神经病变中不可或缺的作用提供了大量证据。

4. 肠道菌群衍生物对 DKD 影响

4.1. LPS

LPS 是失调的肠道菌群死亡、溶解产生的一种肠道内毒素，位于大多数革兰氏阴性菌细胞壁外层。此外，由于 DKD 肠漏综合征的形成，LPS 易位导致 LPS 的高循环水平，一种称为“内毒素血症”的疾病，刺激免疫系统细胞，尤其是巨噬细胞和内皮细胞。Salguero 等[48]揭示了 DKD 患者革兰氏阴性菌的生态失调。与对照组相比，DKD 患者肠道包括*变形菌门*、*疣*菌门和*梭杆菌*的相对丰度增加、LPS 浓度升高以及由 C 反应蛋白(CRP)、TNF-α 和 IL-6 组成的炎症生物标志物的积累状态。此外，LPS 通过 TLR4 介导的 MyD88 和 MD2 信号激活 IL-1R 相关激酶(IRAK)，随后诱导 TNF 受体相关因子 6 (TRAF6)与 IRAK 和其他蛋白结合形成大型复合物，催化 TRAF6 的 Lys 63 连接的多泛素链的合成，最终导致活化的转录因子 NF-κB 和排出的促炎细胞因子[49]，已知这在 DKD 的发病机制中十分重要[50]。

4.2. SCFS

短链脂肪酸是肠道微生物群发酵膳食多糖的最终产物，包括乙酸盐、丙酸盐、丁酸盐、戊酸和异丁酸[51]。SCFA 的功能通常与跨膜 G 蛋白偶联受体(GPR)的激活和组蛋白乙酰化(HDAC)的抑制有关[52]，以及通过 GPR 刺激增加胰高血糖素样肽-1(GLP-1)和 GLP-2 的产生，以及胰岛素表达升高和随之而来的胰岛素敏感性和胰腺细胞增殖的增强。有趣的是，葡萄糖稳态和饱腹感都受到肠道微生物群成分(如*双歧*

*杆*菌和*乳酸菌*)的调节，这些成分可增强 GLP-1 的分泌[53]。此外，短链脂肪酸可以抑制高糖和 LPS 诱导的肾小球系膜细胞的氧化应激和炎症[54]，并改善肠道屏障功能[55]。丁酸钠治疗显著降低血浆中葡萄糖、肌酐和尿素的水平，减弱组织学变化，包括纤维化和胶原沉积，并抑制糖尿病肾脏中 HDACs、eNOS、iNOS、纤连蛋白、TGF-β1、NF-κB、细胞凋亡和 DKDA 损伤的活性[56]。然而，并非所有短链脂肪酸的补救措施都显示出良好的效果。Lu 等[57]发现，与对照组相比，DM 大鼠肠道菌群异常，血浆醋酸盐水平升高，蛋白尿升高，GBM 增厚，肾足细胞足突丢失。此外，DM 大鼠肾脏中血管紧张素 II、血管紧张素转换酶和血管紧张素 II.1 型受体的含量增加，表明肠道菌群紊乱产生的多余乙酸可能通过激活肾脏中的 RAAS 而引起肾脏损伤。据推测，短链脂肪酸研究的这些差异可能是由于不同疾病的不同动物模型以及短链脂肪酸的组别、浓度和应用时间造成的。

4.3. 其他代谢产物

支链氨基酸(BCAA)是由肠道菌群合成的必需氨基酸，包括缬氨酸、异亮氨酸和亮氨酸。支链氨基酸调节蛋白质合成、葡萄糖/脂质代谢、胰岛素抵抗和免疫力，以及维持体内平衡[58]。多胺，如精胺，腐胺，多胺氧化酶和丙烯醛，通过改变肠道微生物群的代谢参与肾脏疾病的发展[59]。

肠道菌群的失调促进了细菌衍生的尿毒症毒素的产生，如硫酸吲哚酚(IS)、内毒素、TMAO 和对甲酚硫酸盐(PCS)，这些毒素增加了肠道通透性，并通过受损的肠道屏障转移到体循环中。尿毒症毒素在肾脏中的积累可能导致肾功能不全[60]。TMAO 是一种肠道微生物群衍生的代谢物，与 1 型糖尿病的死亡率和肾脏结局有关[61]。较高的血清 TMAO 水平增加了血液透析患者腹主动脉风险[62]。硫酸苯酯(PS)导致足细胞损伤和白蛋白尿，并被证明与 DKD 的进展有关[63]。丙酸咪唑是一种由通过肠道微生物群分解组氨酸产生的代谢物，在 2 型糖尿病中增加，影响宿主炎症和代谢[64]。PS 和 TMAO 都可能通过分泌相关衰老表型和慢性低度炎症参与 DKD 的发生[65]。IS 和 PCS 通过激活炎症和氧化应激导致肾脏病和心血管毒性[67]。此外，尿素、TMAO、PCS 和 3-羧酸 4-甲基-5-丙基-2-呋喃丙酸(CMPF)等几种尿毒症毒素与葡萄糖稳态异常和糖尿病发病率有关[67]。

5. 结论与展望

综上所述，肠道菌群失调与 DKD 密切相关，肠道菌群失调和肾脏损害导致有益菌株的丧失、大量尿毒症毒素的积累和尿路感染的发病率增加，加速了 DKD 的进展。基于肠道菌群的治疗可能是未来预防和治疗 DKD 的一种有前途的策略。

然而，在确定微生物群来源或宿主与本身的某些代谢物的潜在因果关系方面，仍有一些复杂性难题需要克服。高质量的微生物组分析工作流程对于获得可靠且可重复的结果十分重要。因此，宏基因组学与代谢组学的结合有助于研究不同细菌和代谢物介导的信号和效应，以及探索细菌群落在治疗相关疾病中的合理应用。肠道微生物群衍生的代谢物可作为 DKD 的生物标志物，用于筛查、诊断和预后 DKD，以及探索 DKD 涉及的分子机制或途径，促进个体化的预防和治疗[68]。同时，目前大多数数据仅限于啮齿动物模型，需要更可靠的临床试验来阐明 DKD 发病机制中的关键途径和特定菌株。针对肠道菌群的治疗策略在未来具有巨大的潜力，将为 DKD 治疗开辟新的视角和方向。

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