·综述·

肠道菌群失衡与糖尿病肾病的关系及中药防治研究进展

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【摘要】肠道菌群作为人体最大的微生物库，种类丰富，与健康和疾病的发生发展密切相关。肠道菌群失衡已被证实与糖尿病肾病（diabetic nephropathy, DN）发病存在相关性，肠道内条件致病菌种类及数量越多，DN 患者肾脏损害越严重。干预肠道菌群结构，增加有益菌群丰度，可有效改善肾脏功能和肾脏病理损害，防治 DN，改善终末期肾脏疾病预后不良。中医药治疗 DN 具有低价效优、不良反应小、靶点多、途径广等优点，在防治 DN 中占据重要地位，且可与西药联合使用，达到取长补短、标本兼治的优势。中医药通过干预肠道菌群治疗 DN 疗效显著，但中医外治法对于 DN 的研究相对有限。本文针对肠道菌群与 DN 的关系及中药活性成分、中药复方及中药灌肠干预肠道菌群的研究进展进行综述，以期为中医药防治 DN 提供参考。

【关键词】糖尿病肾病；肠道菌群；慢性肾脏病；中药

Research progress of the relationship between intestinal flora imbalance and diabetic nephropathy and its prevention and treatment by traditional Chinese medicine

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【Abstract】As the largest microbial pool in human body, intestinal flora is rich in species, which is closely related to the development of health and disease. The imbalance of intestinal flora has been confirmed to be related to the pathogenesis of diabetic nephropathy (DN), and the more types and quantities of intestinal conditional pathogenic bacterium, the more serious renal damage in DN patients. Intervening the structure of intestinal flora and increasing the abundance of beneficial bacteria can effectively improve renal function and

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renal pathological damage, prevent DN and improve the poor prognosis of end-stage renal disease. Traditional Chinese medicine in the treatment of DN has the advantages of low price, good effect, small adverse reactions, more targets and wide channels. It occupies an important position in the prevention and treatment of DN, and can combine with western medicine to achieve the advantages of learning from each other and treating both symptoms and root causes. Traditional Chinese medicine has remarkable therapeutic effect on DN by interfering with intestinal flora, but the research on external treatment of traditional Chinese medicine is relatively limited. This paper reviewed the research progress of the relationship between intestinal flora and DN, and the active ingredients of traditional Chinese medicine, traditional Chinese medicine compound and enema intervention of traditional Chinese medicine on intestinal flora, in order to provide reference for the prevention and treatment of DN by traditional Chinese medicine.

【Keywords】Diabetic nephropathy; Intestinal flora; Chronic kidney disease; Traditional Chinese medicine

糖尿病肾病（diabetic nephropathy, DN）是糖尿病常见并发症，长期糖脂代谢异常导致肾小球基底膜增厚、K–W 结节形成、球性硬化、尿蛋白逐渐增多、肾小球滤过率（glomerular filtration rate, GFR）进行性下降，是发达国家终末期肾病（end–stage renal disease, ESRD）最常见的原因[1]。DN 患者的尿酸、草酸盐等大量代谢废物聚集于结肠，透过肠壁血管进入肠腔，改变肠道环境，进而导致肠道菌群失调[2–3]。现代药理学研究表明，肠道菌群与遗传、环境和饮食等因素一样，在糖尿病的发生发展中起着重要作用[4–5]。近年来，肠道菌群在糖尿病肾脏疾病防治中的作用研究热度日益上升，中医药针对肠道菌群失衡的靶向治疗 DN 成为当前研究的新热点，也是防治 DN 的新途径。糖尿病及其并发症属于中医“消渴”范畴，中医药从临床出发，结合新技术及新方法，发挥自身特色与优势，调控肠道菌群，对防治 DN 起到了重要作用[6–7]。本文总结了肠道菌群与 DN 的关系及中医药干预肠道菌群治疗 DN 的研究进展，旨在为中医药防治 DN 提供参考。

1 糖尿病与肠道菌群紊乱

人体肠道菌群种类超 1 000 种，数量超过 100 亿，除有益菌群（如厚壁菌门、放线菌门）外，还包含致病菌（如大部分变形菌门）、条件致病菌（如部分拟杆菌门），这些菌群在人体内与宿主相互依赖和制约，肠道菌群间的动态平衡与健康和疾病的发生发展密切相关[8–10]。宿主的遗传基因、细菌暴露状态、饮食、吸烟、饮酒和罹患各种疾病等因素均可导致肠道菌群改变，进而引起多种慢性疾病[11–12]，如肠道炎症[13]、2 型糖尿病及其并发症[14]、抑郁症[15]、慢性肾脏病[15]，甚至癌症[16]。

糖尿病的发生是营养过剩引起肠道微生物紊乱的结果之一，营养过剩会严重破坏肠道菌群的多样性和稳定性，使有益微生物区系减少且条件性致病微生物区系增加，引发肠道慢性低度炎症，从而导致糖尿病的发生[17–18]。肠道菌群失调还会导致生化因子波动下降，短链脂肪酸、胆汁酸、内分泌调节多肽（如胰高血糖素、胰高血糖素样肽 –1、胰高血糖素样肽 –2）含量下降，内毒素含量升高，进一步诱发糖尿病[19–23]。反之，平衡的肠道菌群可促进新陈代谢，增强免疫功能，调节肠道菌群可改善肠道状态，增加胰岛素含量，调节血糖，从而改善糖尿病。

2 DN与肠道菌群紊乱

中医认为“正气存内，邪不可干”，正气的充盛依赖于阴阳对立平衡。肠道菌群中的有益菌为阳、有害菌为阴，二者相互制约，达到一种平衡状态；反之，若阴阳平衡失调，就会导致疾病的发生[24]。Meijers 等于 2011 年提出了“肠 – 肾轴”概念[25]，相关研究也揭示了肠道菌群失调可通过调控肠道相关代谢产物（如过量乙酸盐）激活肾素 – 血管紧张素系统，引起早期 DN 的肾损伤[26–27]。但适量丁酸盐作为一种抗炎的短链脂肪酸盐，可为

肠黏膜提供营养，增强肠黏膜免疫[28–29]。研究发现，肠道菌群通过分解食物中的氨基酸产生尿毒症毒素（如吲哚、对甲酚和甲基胆汁酸等），避免因这些毒素导致肾脏损伤和肾功能下降[30]。同时，肾脏疾病患者中肠道炎症和肠道通透性增加，导致肠道细菌及其代谢产物进入血液，从而引发全身性炎症反应。研究证实，DN 患者肠道菌群微生物的丰度和细菌总数与健康人群、糖尿病患者存在显著差异[30–31]。有研究发现，特定菌群与 DN 的发生发展存在相关性，与 2 型糖尿病患者相比，DN 患者的肠道菌群中含有更高水平的埃希氏菌 – 志贺氏菌（Escherichia–Shigella）和更低水平的普雷沃特氏菌 _9（Prevotella_9）[31]。在 DN 中，优势菌群主要为拟杆菌属，占总数的 90% 以上，且肾脏功能损害越重，肠道菌群里的条件致病菌数量越多[32–33]。以上研究结果说明肠道菌群不仅参与 DN 的发生发展，还在其中起着重要作用。

3 中医药干预肠道菌群防治DN

近年来研究发现，中医药可通过提高肠道内有益菌群丰度，降低有害菌群丰度，增加肠道菌群多样性和有益菌 / 有害菌比，调整肠道菌群结构，逆转肠道菌群失衡，改善肠道屏障和减轻肠道炎症，起到改善 DN 的作用[34–35]。

3.1 中药单体及提取物

张文杰等研究发现，山药多糖可干预 DN 大鼠肠道菌群和改善肾功能，随着山药多糖浓度增加，厚壁菌门等有益菌丰度不断增加，而拟杆菌门、变形菌门等有害菌群数量不断下降，且 DN 大鼠 24 h 尿蛋白、血清肌酐、血清尿素氮等指标得到改善，肾损伤状态得以缓解[36]。蔡红蝶等研究发现，丹参水提物、丹参醇提物及黄葵胶囊均可干预肠道菌群丰度，增加有益菌群数量，改善肾功能和肾损伤状态[37]。Yang 等研究发现，冬虫夏草多糖可减少 DN 大鼠肠道菌群多样性，增强肠道有益菌群增殖能力、提高有益菌群的相对丰度，同时还可抑制肾脏炎症、成纤维细胞活化，达到保护肠道菌群状态、维持肠道微生物系统动态平衡、保护肾脏、防治 DN 的作用[38]。Cai 等研究发现，白藜芦醇可改善 DN 小鼠肠道屏障，逆转有益菌群丰度低下状态，增加肠道细菌多样性，虽然致病菌变形菌属的丰度下降不明显，但白藜芦醇在缓解肾脏炎症、防治 DN 方面效果较优[39]。

山药多糖、丹参及黄葵胶囊、冬虫夏草多糖及白藜芦醇等中药单体及提取物能够调节肠道菌群的丰度和多样性，增加有益菌群数量，减少有害菌群，同时还可改善肾损伤状态，包括减少尿蛋白、降低血清肌酐和血清尿素氮水平，说明中药单体及提取物在保护肠道菌群平衡、维护肾脏健康、防治 DN 方面有潜在作用。

3.2 中药复方及中成药

姚宇剑等研究发现，缩泉益肾方可以调整 DN 小鼠肠道微生物的结构组成，增加有益菌群相对丰度，减少致病菌群相对丰度，降低厚壁菌门与拟杆菌门的比值，同时降低尿白蛋白、尿肌酐及血糖，改善肾损伤状态，对 DN 产生治疗作用[40]。Chen 等实验发现，补肾活血方增加了 DN 小鼠有益菌群的相对丰度，有效降低了类杆菌门的相对丰度，且核转录因子 –κB（nuclear transcription factor–κB, NF–κB）、白介素 –1β 的相对丰度与蛋白表达呈正相关，表明补肾活血方防治 DN、抗炎作用与调节肠道菌群密切相关[41]。Wei 等研究发现，芪地糖肾颗粒可明显增加 Allpraevotella 丰度，降低乳酸杆菌和细菌的丰度，对 DN 小鼠具有良好的治疗作用，缓解其肾脏损伤，这说明芪地糖肾颗粒对 DN 的治疗作用与干预肠道菌群结构有相关性[42]。Zhao 等研究发现，糖肾方可提高放线菌门双歧杆菌属丰度，减少变形菌门肠杆菌科菌数，重建肠道菌群结构，减少肠道毒素的产生，明显改善 DN 肾脏损伤和肾功能[43]。Gao 等研究发现，经清热消正方治疗的 DN 小鼠肠道中类杆菌丰度显著降低，而细菌、变形杆菌和螺形杆菌丰度较高，提示清热消正方可保护肠道屏障，减轻肠道内毒素产生，并改善肾功能异常和肾脏损伤[32]。Su 等研究发现，三黄益肾胶囊可影响 DN 大鼠肠道微生物群落的 β 多样性，乳杆菌、球形菌、厌氧弧菌和类杆菌相对增多，降低了假丝酵母菌、密螺旋体和硫化弧菌的丰度，同时揭示了三黄益肾胶囊对 DN 的多种改善作用，如降低高血糖和改善肾功能、肾脏病理改变、氧化应激和炎症反应等[44]。王毅强等研究发现，金匮肾气丸能够显著增加阴阳两虚型 DN 患者 Prevotella_7 相对丰度，上调肠道菌群对碳水化合物的代谢效率，改善 DN 患者临床症状、肾功能和血糖水平[45]。

总体而言，上述中药方剂均能够调整肠道微生物结构，增加有益菌群的相对丰度，减少致病

菌群的相对丰度，同时对肾脏健康有积极影响，包括降低尿白蛋白、尿肌酐、血糖水平，改善肾脏损伤状态。这些中药的治疗效果与其对肠道菌群结构的调节密切相关，包括增加有益菌群数量、减少有害菌群相对丰度、调整菌群多样性，以上研究结果为中药治疗 DN 的潜在机制研究提供了参考。

3.3 中药灌肠

肠道菌群失调是 DN 发展的一个重要因素，DN 患者肠道内有益菌群数量明显减少，肠道菌群处于一种失调状态[2, 46]。中药灌肠可通过直接干预肠道菌群结构调节肠道菌群状态，从而改善 DN。Ji 等研究发现，大黄干预可改善肠道屏障，调节肠道菌群 Akkermansia、Methanosphaera 和 Clostridiaceae 失调，同时抑制 Toll 样受体 4（TLR4）–髓样分化因子 88（MyD88）–NF–κB 炎症反应，抑制全身炎症，减轻肾纤维化[47]。徐艳文等研究发现，糖肾涤肠方联合缬沙坦可有效治疗 DN 患者，治疗有效率达 92%，临床症状及体征基本消失，尿白蛋白排泄率基本恢复正常，24 h 尿蛋白定量下降≥ 50%[48]。冯程程通过动物实验发现，糖肾灌肠方可干预 DN 小鼠肠道菌群结构，提高有益菌群厚壁菌门丰度，且厚壁菌门占全部菌落的 43%，有害菌群拟杆菌门和变形菌门丰度下降[49]。

中药灌肠作为一种直接干预肠道菌群结构的方法，对改善 DN 患者肠道菌群状态具有潜在疗效。大黄、糖肾涤肠方、糖肾灌肠方等能够改善肠道屏障，调节肠道菌群结构，提高有益菌群丰度，降低有害菌群丰度，减轻全身炎症，改善临床症状，恢复尿白蛋白排泄率。但关于中药灌肠治疗 DN 的研究相对较少，目前相关机制有待明确，后续需深入研究，为中医灌肠疗法治疗 DN 奠定理论基础。

4 小结

综上所述，本文通过探讨肠道菌群与 DN 的关系，总结了中药调节肠道菌群失衡治疗 DN 的研究现状，旨在发挥中药价廉效优、不良反应小且具有多个作用靶点、途径和层次的优势。干预肠道菌群失衡状态能够降低血糖、减轻肾间质纤维化、改善全身微炎症状态，进而改善终末期肾脏疾病预后。然而，特定菌群的存在或缺失是否与 DN 的发生发展有关、菌群代谢产物与 DN 发生机制的关系、探索微生物组转移疗法作为治疗 DN 的潜在手段、通过改变患者肠道菌群影响疾病进展的可能性、中药如何干预肠道菌群群落变化等相关研究相对较少，有待进一步研究探讨。未来的研究应紧扣研究前沿，采用新技术及新方法，探索尚未明确的具体作用机制，并进行长期的随访研究和大规模的临床试验，以验证肠道菌群在 DN 防治中的效果，为中医药应用于临床治疗 DN 提供可靠的理论依据和参考。

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