糖尿病肾病的发病机制及治疗进展

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摘要: 糖尿病肾病是糖尿病重要的微血管并发症, 可进展为终末期肾病, 严重威胁患者生存质量与寿命。糖尿病肾病的发病机制复杂, 涵盖炎症反应、氧化应激、代谢紊乱及肾脏细胞间信号网络失衡等多重环节, 并显著受到个体差异的影响。目前临床治疗手段有限, 尚缺乏针对性的有效药物, 给防治带来巨大挑战。本文系统综述了糖尿病肾病的发病机制和现有治疗策略, 并结合最新进展探讨了新兴治疗思路与潜在突破方向, 以期为创新干预手段和临床转化提供理论与实践基础。

关键词: 糖尿病肾病; 发病机制; 代谢紊乱; 临床治疗; 新兴疗法

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Pathogenesis and therapeutic advances in diabetic kidney disease

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Abstract: Diabetic kidney disease is a significant microvascular complication of diabetes that can progress to end-stage renal disease, severely threatening patients' quality of life and longevity. Its pathogenesis is complex, involving multiple pathways including inflammatory responses, oxidative stress, metabolic disorders, and disrupted intercellular signaling networks in the kidney, all significantly influenced by individual variability. Current clinical treatment options remain limited, with a lack of targeted effective drugs posing substantial challenges for prevention and management. This systematic review examines the pathogenesis and existing treatment strategies for diabetic kidney disease. By integrating recent advances, it explores emerging therapeutic approaches and potential breakthrough directions, aiming to provide a theoretical and practical foundation for innovative interventions and clinical translation.

Key words: diabetic kidney disease; pathogenesis; metabolic disorder; clinical treatment; emerging therapy

随着社会的快速发展和人类饮食结构的改变, 糖尿病 (DM) 发病率显著上升, 是与心血管疾病、癌症、慢性呼吸道疾病并列的影响人类健康的四大慢性非传染性疾病[1]。DM是一种以血糖浓度升高、胰岛β细胞受损、糖脂代谢紊乱为特征的慢性疾病, 统计数据显示, 2024年全球糖尿病患者约5.89亿人, 预计到2050年将增至13.1亿人, 凸显其日益严峻的公共健康挑战[2]。国际糖尿病联合会 (IDF) 的数据表明, 中国是全球糖

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尿病患者最多的国家[3]。DM相关死亡主要由动脉粥样硬化性心血管疾病驱动。此外, 微血管并发症 [包括糖尿病肾病 (DKD)、视网膜病变、神经病变] 亦增加致残及死亡风险[4]。在DM诸多并发症中, DKD是最常见的微血管并发症之一, 也是导致终末期肾病 (ESKD) 的主要原因。有研究表明, 中国2型糖尿病 (T2DM) 患者的DKD患病率达21.8%, 超越慢性肾小球肾炎, 成为我国慢性肾脏病的主要病因[5]。

DKD的致病因素与发病机制呈现高度复杂性, 涉及糖脂代谢紊乱、遗传易感性、氧化应激–炎症通路交互作用及表观遗传调控异常等多重病理过程。现阶段临床治疗手段主要聚焦于代谢调控和肾素–血管紧张素–醛固酮系统 (RAAS) 抑制等, 但在延缓疾病向ESKD进展方面仍面临诸多挑战, 这凸显了现有疗法的局限性和对新靶点和新策略的迫切需求。本文旨在系统梳理DKD的核心发病机制与新兴疗法的进展, 以期为创新干预策略的开发和临床转化提供理论基础。

1 糖尿病肾病的发病机制

DKD的主要病理特征为肾小球系膜基质增多、基底膜增厚、肾小动脉玻璃样变、肾小管变形和肾小囊滴状病变[6], 其临床定义为肾小球过滤率 (GFR) 降低或者尿蛋白排泄升高, 并以尿白蛋白排泄 > 30 mg·d^{-1} 作为诊断标准。因此, 阐明上述病理变化背后的驱动机制, 对于开发新的防治策略至关重要。

1.1 遗传因素与表观遗传调控

DKD并非单基因遗传病, 而是由多个微效基因构成的复杂网络共同调控[7]。有证据表明, DKD在T2DM人群中存在一定的家族聚集性[8]。近年来, 全基因组关联研究 (GWAS) 以及表观遗传修饰在DKD发病机制中的作用逐渐受到关注, 已经有研究证实RAAS中血管紧张素转换酶 (*ACE*) 基因的多态性与DKD的发生相关[9]; 在糖代谢中, *GCKR*基因的多态性可能通过影响糖酵解稳态间接促进肾脏微环境的代谢应激[10]; 而*TCF7L2*作为Wnt信号通路的关键转录因子, 其变异与β细胞功能衰退和糖代谢紊乱密切相关[11]; GWAS还证实*SLC12A3*基因编码的钠–氯协同转运蛋白是肾小管重吸收功能的关键执行者, 其突变直接关联于中国人群的DKD进展[12,13]。此外, *APOE*、*APOC3*和*ADIPOQ*等基因不仅在脂质代谢过程中发挥重要的作用, 其突变还与DKD易感性的个体差异相关[14-16]。

DKD的遗传易感性源于一个由多基因构成的复杂网络。早期的GWAS成功鉴定出包括*CARS*、*FRMD3*、*GCKR*、*TCF7L2*等在内的众多易感位点[10]。然而, GWAS本身存在局限: 它往往只能将风险定位到基因组的一个“街区”, 却难以精确指认具体的“肇事基因”及其作用的“细胞房间”。近年来, 单细胞测序与空间转录组学技术的兴起, 使研究者能够以一个全新的视角来解读遗传的风险。如通过单细胞测序发现, DKD的疾病进展以及药物的治疗反应具有高度的细胞类型特异性, 鉴定出在人类DKD中同样存在的损伤近端小管细胞亚群, 还通过精准的细胞类型解析, 揭示了钠–葡萄糖协同转运蛋白2抑制剂 (SGLT2i) 的作用与近端小管S1段中剪接因子Srsf7的表达调控密切相关[17]。最近的空间多组学研究揭示了DKD肾脏中纤维化微环境的精确细胞构成与空间组织, 并鉴定出嵌入该环境中的损伤小管细胞亚型 (HAVCR1 + iPT) 是驱动疾病进展的关键因素[18]。基于此构建的FME基因标签也具有预后预测能力, 这标志着DKD研究正从传统的组织形态学分析, 迈向基于空间分子分型的精准医学时代。

1.2 氧化应激

维持健康肾脏正常的工作需要大量的能量, 因此肾脏拥有仅次于心脏数量的线粒体。活性氧 (ROS) 的来源除线粒体之外还包括葡萄糖的自氧化以及烟酰胺腺嘌呤二核苷酸磷酸还原氧化酶的酶促途径[19]。ROS可以作为第二信使调节多条信号通路, 也可以作为免疫细胞代谢、激活、增殖、分化和凋亡的调节因子[20]。当ROS过量生成并打破氧化/抗氧化系统平衡时, 即形成氧化应激, 导致组织损伤[21]。

在机体长期高血糖的状态下, 葡萄糖代谢途径异常导致ROS大量累积破坏肾脏细胞的结构和功能, 尤其是肾小球细胞更为敏感[22]。过量的ROS可激活炎症通路和RAAS系统, 引发炎症细胞浸润, 促进炎症因子 (TNF-α、IL-1, 6, 18) 和血管紧张素Ⅱ (AngⅡ) 释放[23], 加重肾脏损伤并促进DKD进展。氧化应激还会刺激系膜细胞增殖和细胞外基质分泌, 促进肾小管间质纤维化, 并通过线粒体ROS-TXNIP/NLRP3/IL-1β轴介导肾小管损伤[19]。

此外, 持续的高血糖状态还会增加晚期糖基化终末产物 (AGEs) 的产生, AGEs与RAGEs相互作用, 激活过氧化物酶体增殖物γ受体 (PPARγ), 刺激细胞内产生ROS[24]。AGEs增加还会刺激肾小球细胞产生TGF-β1, 导致肾小球硬化和间质性肾小管损伤, 并进一步激活NF-κB和蛋白激酶C (PKC) 等信号通路[25]加重炎症反应和纤维化。

1.3 糖代谢紊乱

在DKD的发病过程中, 持续的高血糖不仅是代谢失衡的标志, 还可以通过生成多种毒性中间代谢产物, 对肾脏细胞造成损伤。近年研究日益揭示, 这些看似

独立的糖代谢紊乱通路, 最终汇聚并协同放大炎症、氧化应激及纤维化等核心致病环节, 构成一个复杂的损伤网络。

1.3.1 AGEs的激活 在缺乏酶催化的条件下, 葡萄糖可与生物大分子的自由氨基发生非酶促糖基化反应, 形成不稳定的Schiff碱[26], 继而在糖基化的早期阶段重排形成Amadori产物; 在晚期阶段, Amadori产物经氧化、脱水、分子重排等形成稳定不可逆的AGEs[26]。AGEs可以通过与肾小球基底膜中的胶原蛋白进行交联, 使其弹性和通透性下降[27], 从而诱发蛋白尿。足细胞中的蛋白质被AGEs修饰后直接诱发内质网应激与线粒体功能障碍, 导致足细胞的凋亡[28]。AGEs通过与RAGE结合可以放大炎症信号, 启动NF-κB信号通路, 上调包括白细胞介素-1β在内的多种促炎因子表达, 并促进ROS的产生[29]; 同时还有证据表明, AGE-RAGE轴是“代谢−炎症”对话的关键枢纽, AGE-RAGE信号通路通过介导NLRP3炎症小体的组装与激活, 将代谢应激转化为炎症反应[30]。

1.3.2 多元醇通路与蛋白激酶C的激活 多元醇信号通路在高血糖状态下会被显著激活, 导致NADPH大量消耗。NADPH是维持细胞内抗氧化剂谷胱甘肽还原状态的关键辅酶, 其耗竭直接削弱细胞的抗氧化能力, 造成氧化应激水平急剧升高[31]。与此同时, 高血糖衍生的二酰甘油 (DAG) 合成增加, 异常激活PKC的多种亚型如PKCβ和PKCδ, 上调TGF-β、VEGF的表达和细胞对TGF-β的敏感性, 促进了细胞外基质的产生; PKCα和β与激活NADPH氧化酶产生的ROS有关, 从而引起肾损伤[32]。

因此, 多元醇通路与PKC通路共同汇聚于氧化应激这一关键节点, 形成一个自我放大的恶性循环。过量的ROS不仅直接损伤DNA、蛋白质和脂质, 还作为第二信使, 激活NLRP3炎症小体、促纤维化因子TGF-β, 并增强VEGF表达, 改变肾小球血流动力学, 共同推动DKD的进展[33]。

1.4 脂代谢紊乱

肾脏作为高代谢活性器官, 维持其正常的工作运转需要持续且充足的能量供应, 其中大部分的能量来源是脂质氧化[34]; 在DKD中, 脂代谢紊乱不仅关乎能量供应失调, 其导致的肾脏脂质异常积聚 (脂毒性) 是直接驱动细胞损伤和炎症的独立致病因素[35]。

1.4.1 肾脏胆固醇代谢紊乱 DKD患者肾活检中可观察到大量脂质沉积和细胞内脂滴增加, 其核心在于胆固醇外排受阻与摄取增加之间的失衡[36]。机体高血糖状态会减少三磷酸腺苷结合转运蛋白A1的表达, 同时CD36介导的脂质摄取可能增强, 导致胆固醇稳态失调, 肾小球内皮细胞受损[37]。过量的游离胆固醇整合到内质网膜中, 破坏其结构, 引发未折叠蛋白反应 (UPR)。持续的UPR会启动CHOP介导的凋亡信号通路[38]。此外, 胆固醇在细胞内堆积会形成胆固醇结晶, 激活NLRP3炎症小体, 导致Caspase-1切割和IL-1β等促炎因子的成熟与释放, 在局部形成炎症微环境。

1.4.2 脂肪酸代谢紊乱 代谢组学研究表明, DKD患者体内的关键转录调控因子PGC-1α和PPAR-α的表达下降, 导致其下游靶基因 (如CPT-1) 表达受抑, 限制了脂肪酸进入线粒体进行β-氧化的能力, 导致ATP生成不足, 能被氧化的脂肪酸 (如棕榈酸) 转而合成神经酰胺、DAG等具有生物毒性的脂质中间产物, 进一步损害线粒体的功能, 最终启动线粒体途径的内源性凋亡[39]。同时也有研究在DKD小鼠肾脏中定位了5条功能失调的代谢途径, 其中两条与脂肪酸的合成和降解相关, 揭示了DKD进展过程中从代谢物到酶的分子水平的变化[40]。

1.5 炎症反应

在DKD发生发展的进程中, 由糖脂代谢紊乱所触发的慢性炎症是驱动肾脏损伤的核心环节。这一过程始于代谢应激对固有免疫系统的激活, 继而通过关键炎症平台与因子网络放大信号, 最终导致免疫细胞浸润和组织结构的不可逆损害。

1.5.1 炎症的代谢性触发与核心平台: NLPR3炎症小体 如前文所述, 在DKD的发病进程中, 糖脂代谢紊乱、氧化应激和AGEs贯穿始终, 通过诱导线粒体功能障碍产生ROS及形成胆固醇晶体等途径, 直接激活NLRP3炎症小体。其活化导致Caspase-1介导的IL-1β和IL-18成熟与释放, 诱导细胞焦亡, 加重组织炎症损伤。有研究表明, NLRP3炎症小体被激活的高血糖小鼠其肾小球系膜扩张, 肾小球基底膜厚度增加[41,42], 加重足细胞损伤并诱发肾间质纤维化[43]。

1.5.2 关键炎症因子网络 同种异体炎症因子-1 (AIF-1) 是一种调节炎症反应和免疫反应的蛋白质[44], 在DKD小鼠肾小球内皮细胞中高表达, 在高糖环境中AIF-1可以通过激活NF-κB信号通路促进DKD中的肾小球内皮细胞炎症和氧化应激[45]。Hao等[46]研究发现, AIF-1可通过调控miR-34a/ATG4B通路, 影响肾小球内皮细胞的自噬水平, 从而在炎症、氧化应激之间形成复杂交互, 共同推动DKD进展。

TNF-α作为一种多功能的细胞因子, 可以诱导巨噬细胞分化以及其他多种细胞因子的产生。临床数据分析显示, DKD患者的血清TNF-α水平显著高于健康人群和单纯的DM患者[47], 并且与肾脏的损伤程度相关[48]。Nishad等[49]研究表明足细胞分泌的TNF-α是招

募巨噬细胞迁移、导致肾脏炎症的重要信号。

白细胞介素 (IL) 是指一类分子结构和生物学功能已明确且具有重要调节作用统一命名的细胞因子。多种IL在DKD中扮演不同的角色。肾小球中IL-33显著上调提示其参与肾小球内皮炎症, 而阻断其通路可起到保护作用[50]; IL-6在所有类型的肾脏细胞中高表达时会导致内皮改变、足细胞损伤、肾小球肥大和系膜纤连蛋白表达增加[51], 因此IL-6被广泛认为是加速DKD进程的重要因素。临床研究也证实IL-6、IL-8和IL-10联合检测的方法, 能够较为准确地反映出DKD患者的肾功能损伤程度[52]。

1.5.3 免疫细胞的浸润与终末损伤 前述炎症因子网络招募并激活了各类免疫细胞, 形成炎症浸润的终末执行阶段。DKD患者的肾脏中常有单核细胞、巨噬细胞等免疫细胞的浸润, 巨噬细胞通过释放TNF-α、IL-1β、IL-6等促炎性细胞因子, 激活局部炎症反应[53], 加剧肾小球和肾小管的损伤。此外, 适应性免疫应答也被激活, Th17细胞通过分泌IL-17, 诱导巨噬细胞和中性粒细胞的浸润, 而树突状细胞会促进Th1和Th17细胞的分化[54], 进一步放大炎症反应。这种由固有免疫到适应性免疫的过度活化, 共同导致了进行性的肾小球硬化和肾间质纤维化, 最终驱动DKD走向ESKD。

DKD的病理生理机制错综复杂, 是多种信号通路协同作用的结果。综上所述, DKD的核心发病机制可归纳为图1。

2 糖尿病肾病的临床治疗方法

近年来, DKD的临床治疗策略取得了一定的进展, 已从单纯控制血糖、血压的传统模式, 逐步转变为以延缓疾病进展、降低心肾终点事件风险为目标的器官保护新模式。血管紧张素转换酶抑制剂 (ACEI) 和血管紧张素II受体拮抗剂 (ARB) 作为基础治疗药物的地位已确立多年。然而, 随着大量循证医学证据的积累, 一系列新型药物因其卓越的心肾保护作用也获得了FDA的批准, 包括SGLT2i、盐皮质激素受体拮抗剂 (MRA) 和GLP-1受体激动剂 (GLP-1 RA)。这些药物通过不同机制多靶点干预DKD的病理过程, 在改善代谢的同时显著降低心肾结局风险。其主要作用机制与临床疗效总结如下 (表1)[55-58]。

2.1 SGLT2i

SGLT2i是一种不依赖于胰岛素的新型降糖药物, 如达格列净、恩格列净、卡格列净等; 其作用机制为通过糖苷配基与SGLT2发生竞争性结合, 特异性抑制SGLT2在肾近端小管中的活性, 减少肾小管上皮细胞对葡萄糖的重吸收, 促进尿糖排泄从而发挥降糖作用[59]。除上述经典途径外, 近期临床前研究揭示了其更为深层的分子机制。SGLT2i能够激活AMPK信号并抑制mTORC1的活性, 进而下调促炎细胞因子与黏附分子的表达[60]。同时, 它们还可能通过减轻氧化应激与炎症, 缓解T2DM和CKD患者中常见的交感神经过度兴奋[61]。这些发现表明, SGLT2i的获益远不止于血流动力学改善, 还涉及对肾脏损伤相关细胞内途径的直接调控。

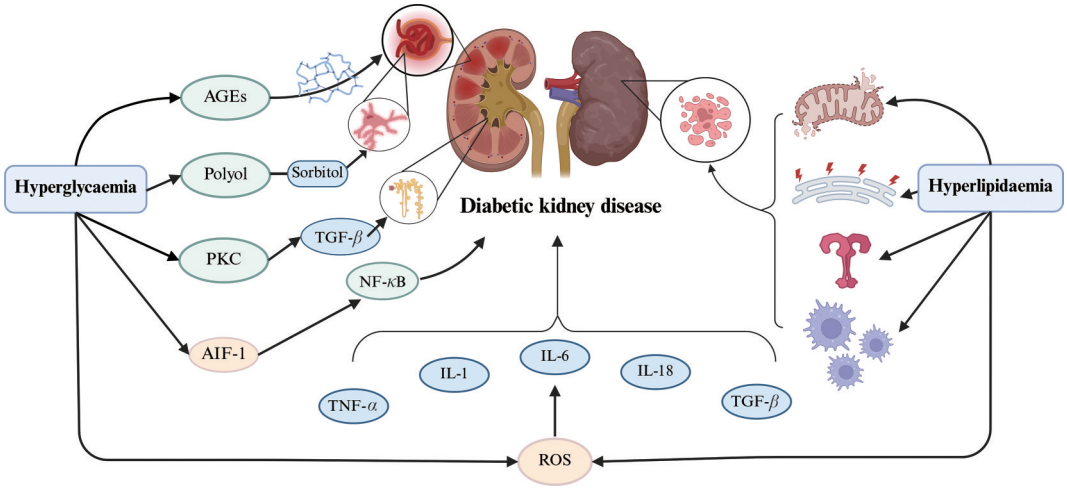


Figure 1 Core pathogenesis of diabetic kidney disease (created by BioRender). Persistent hyperglycemia activates the polyol pathway and protein kinase C (PKC) pathway while promoting the accumulation of advanced glycation end products (AGEs). Hyperlipidemia induces mitochondrial dysfunction, endoplasmic reticulum stress, and macrophage infiltration, thereby promoting the release of multiple inflammatory and pro-fibrotic factors. These mechanisms collectively lead to damage of the glomerular filtration barrier, podocyte detachment, mesangial matrix proliferation, and tubulointerstitial fibrosis, ultimately resulting in proteinuria and progressive renal dysfunction

Table 1 Core mechanisms and primary efficacy of drugs used in the clinical treatment of diabetic kidney disease. ACEI: Angiotensin converting enzyme inhibitor; ARB: Angiotensin receptor blocker; UACR: Urinary albumin creatinine ratio; eGFR: Estimated glomerular filtration rate; ESKD: End stage renal disease

Treatment category	Representative drug	Core mechanism	Primary therapeutic effect	Precaution	Reference
RAAS inhibitor	ACEI: Ramipril, benazepril ARB: Valsartan, losartan	Blocking the renin-angiotensin system reduces glomerular pressure, thereby decreasing proteinuria and fibrosis	UACR reduced by 30%−40%, with annual eGFR decline slowed to −4.4 mL·min^{-1}; cardiovascular event risk reduced by 27%, heart failure risk by 85%, and ESKD risk by 30%	Decreased renal function leads to reduced potassium excretion (hyperkalemia); RAAS blockade inhibits aldosterone secretion	[55]
SGLT2 inhibitor	Dapagliflozin, empagliflozin, canagliflozin	Inhibit glucose reabsorption in the proximal renal tubules, improve tubular hyperfiltration, and alleviate inflammation and oxidative stress	A 30% reduction in the risk of the primary composite endpoint (end-stage kidney disease, renal or cardiovascular death); a 39% reduction in the risk of hospitalisation for heart failure	Monitor renal function changes during the initial phase of treatment Increased risk of genitourinary infections	[56]
Non-steroidal MRA	Finasteride	Selectively inhibit mineralocorticoid receptors to block inflammatory (NF-κB/JAK-STAT) and fibrotic (TGF-β) pathways	The primary composite endpoint (renal failure, eGFR decline ⩾ 40% from baseline, renal-related death) showed an 18% reduction in risk; the key secondary cardiovascular outcomes (cardiovascular death, non-fatal myocardial, non-fatal stroke, heart failure hospitalisation) demonstrated a 14% reduction in risk	May result in hyperkalaemia	[57]
GLP-1 agonist	Semaglutide	Activate GLP-1 receptors, improve insulin sensitivity, and alleviate renal inflammation and fibrosis	A 24% reduction in the risk of renal composite endpoints (eGFR decline ⩾ 50%, renal failure, or renal-related death); an 18% reduction in the risk of major adverse cardiovascular events	Gastrointestinal reactions (nausea/diarrhoea)	[58]

2.2 MRA

非奈利酮 (finerenone, FIN) 是一种新型MRA, Yao等[62]发现FIN治疗可减少暴露于高糖环境中的HK-2细胞和DM小鼠肾小管细胞中的氧化应激、线粒体碎片和细胞凋亡, 并通过PI3K/Akt/eNOS信号通路恢复线粒体自噬。同时在醋酸脱氧皮质酮联合单侧肾切除术 (DOCA/UNX) 小鼠模型中FIN可以降低小鼠的尿白蛋白/肌酐比率, 减少了DOCA/UNX诱导的心脏肥大、心脏纤维化, 起到一定的心、肾保护作用[63]。FIDELIO-DKD和FIGARO-DKD的III期临床试验证明了其在延缓DKD进展和降低心血管事件风险方面的显著疗效[64], 并于2021年被FDA批准用于治疗DKD。

2.3 ACEI/ARB

基于循证医学证据及国际指南共识, RAASi包括ACEI或ARBs, 被确立为DKD患者高血压管理的首选药物, 特别是存在病理性白蛋白尿 (UACR ⩾30 mg·g^{-1}) 的个体中[65]。在一项针对明显DKD合并高血压的患者中, 直接应用ACEI或者ARBs可以观察到其肾脏保护作用[66], 并降低DKD患者的ESRD风险[67], 但同时应该警惕高血钾症和血肌酐的一过性升高[68]。ACEI/ARB与SGLT2i联用可以进一步降低UACR和收缩压, 延缓eGFR下降, 但低血糖风险增加37%。

2.4 GLP-1 RA

GLP-1是一种在临床实践中使用的新型抗糖尿病药物, 越来越多的证据表明, GLP-1 RA可能对DKD具有一定的治疗作用。近期公布的FLOW试验首次专门评估了GLP-1 RA对肾脏硬终点的影响。在这项针对3 533名2型糖尿病合并CKD患者的研究中, 与安慰剂相比, 索马鲁肽 (Smg) 使主要复合肾脏结局风险降低24%, 且这一获益在接受SGLT2i治疗的患者中同样显著[69]。该研究证实了GLP-1 RA在延缓DKD进展中的独立价值, 为其在CKD治疗中的应用提供了高级别循证证据。Tian等[70]则通过转录组学分析得到索马鲁肽可以通过抑制铁死亡来减轻肾脏的炎症和纤维化。FDA于2025年1月18日批准司美格鲁肽可用于降低2型糖尿病合并CKD患者的肾脏疾病进展、ESKD及心血管死亡风险。

综上所述, SGLT2i、GLP-1 RA、FIN等药物通过各自独特的机制发挥治疗DKD的作用。然而, DKD复杂的病理网络决定了单一疗法往往难以全面遏制疾病进展。因此, 现代治疗策略的核心已从选择单一药物转向构建具有协同效应的多药联合方案。这种策略旨

在通过同时干预血流动力学、代谢紊乱、炎症及纤维化等核心病理环节, 实现最大程度的心肾保护。为清晰展示当前主流的联合治疗策略, 其联用方式及协同机制总结如下 (表 2)[71-75]。

3 糖尿病肾病治疗新视角

3.1 肠道菌群与糖尿病肾病

越来越多研究证明, 肠道和肾脏之间存在一定的相互作用 (肠肾轴), 即肠道菌群及其代谢产物可能会影响肾脏的结构和功能, 同时肾脏疾病的发生也会进一步影响肠道菌群的结构组成。Han 等[76]研究发现, DKD 患者的肠道菌群发生以 *Hungatella* 属和 *Escherichia* 属的富集和产丁酸菌的减少为特征的改变, 并且与健康对照相比, DKD 患者肠道中的微生物丰富度显著降低, 提示这可能与 DKD 的发生发展有关。短链脂肪酸 (SCFAs) 是细菌碳水化合物、膳食纤维发酵的最终产物, 也是肠道菌群重要的代谢产物之一。不同种类的 SCFA 具有不同的功能, 如乙酸、丁酸等具有抗氧化、保护肠道屏障的功能; 有研究证明丁酸盐可通过抑制肾脏 SDF-1 来恢复肾功能, 减轻肾脏炎症[77]。

肠道菌群失调可能会引起代谢紊乱, 如糖代谢紊乱、脂代谢紊乱等, 从而导致 DKD 的发生和发展。Hu 等[78]研究发现肠道菌群产生的乙酸盐可以通过激活 GPR43 介导胆固醇稳态失调, 从而导致肾小管间质损伤。此外, 肠道菌群失调会导致肠道通透性增加, LPS 等内毒素进入血液循环, 结合 Toll 样受体 4 激活免疫细胞, 释放炎症因子 (如 IL-1β、IL-6、TNF-α), 促进肾脏局部炎症和纤维化[79]。Chen 等[80]研究表明汤肾方对 DKD 具有一定的抗炎作用, 同时可以重塑肠道菌群结构, 纠正代谢紊乱。因此, 对肠道菌群进行重编程 (上调益生菌的比例), 或通过粪菌移植恢复肠道菌群平衡可能是 DKD 预防和治疗的新策略[81]。但仍需认识到, 菌群的组成由于受到饮食、基因、抗生素等影响具有高度的个体化, 因此一刀切的益生菌或者益生元的治疗方案具有不稳定性。并且, 关于肠道菌群与肾脏疾病的多数研究停留在使用 16S rRNA 等技术的相关性层面, 菌群紊乱之于 DKD 是“因”还是“果”仍需要宏基因组学、整合代谢组学等技术进行更多的机制研究证实。此外, 粪菌移植存在潜在感染和长期安全性未知等风险, 因此未来应更聚焦于发现菌群代谢产物的关键受体与通路, 开发小分子药物, 以规避活菌移植的不确定性[82]。

3.2 干细胞治疗

DKD 的核心病理特征决定了现有疗法仅能延缓疾病的进展, 无法对已经损伤的肾单位进行修复。近些年来的研究表明干细胞疗法在 DKD 的干预中展现出潜在的治疗效果。干细胞以其多向分化潜能、免疫调节特性及旁分泌效应, 能够有效改善肾脏纤维化、减轻炎症反应, 并在一定程度上促进肾组织功能修复, 为这一难治代谢性肾病提供了新的治疗思路。

间充质干细胞 (MSC) 分布于许多组织和器官中, 是研究最广泛的多能干细胞[83], 其可以植入肾脏, 改善肾功能, 再生肾小球结构, 减少肾间质纤维化, 从而有效治疗 DKD[84]。Chen 等[85]研究表明, 脐带间充质干细胞 (UC-MSCs) 可以通过部分抑制 TXNIP 上调发挥抗凋亡特性以减轻 DKD 大鼠的肾细胞损伤和白蛋白尿。

Table 2 Combination therapy strategies for diabetic kidney disease

Combined strategy	Representative drug combination	Coordination mechanism	Clinical precaution	Reference
Cornerstone combination	RAASi + SGLT2i	Synergistic reduction of intraglomerular pressure Multiple metabolic benefits: SGLT2i deliver additional advantages in blood glucose control, weight reduction, and uric acid reduction	Monitor serum potassium and eGFR Monitor for genital tract infections	[71,72]
Enhanced cardio-renal metabolic combination therapy	SGLT2i + GLP-1 RA	SGLT2i focus on hemodynamics and energy expenditure; GLP-1 RA emphasize central appetite suppression, potent glucose control, and anti-inflammatory effects Synergistic cardio-renal protection: both agents demonstrate independent cardio-renal benefits in large-scale CVOTs	Gastrointestinal reactions indicated for patients requiring potent glycemic control, weight reduction, and cardiovascular and renal protection	[73]
Enhanced combination therapy for anti-inflammatory and anti-fibrotic effects	RAASi/SGLT2i + finerenone	Target synergy: RAASi/SGLT2i improve hemodynamics and metabolism; finerenone directly inhibits mineralocorticoid receptors, delivering potent anti-inflammatory and anti-fibrotic effects This approach simultaneously intervenes across three pathways: hemodynamics, metabolism, and inflammation	Potassium levels must be closely monitored, especially when combined with RAASi Indicated for T2D-kidney disease patients (eGFR $\geqslant$ 25 mL·min^{-1}·1.73 m^{-2}, UACR $\geqslant$ 30 mg·g^{-1}, and high cardiovascular risk)	[74,75]

并有研究发现胎盘衍生的MSCs可以通过调节SIRT1/FOXO1通路, 增强足细胞自噬来改善DKD大鼠的肾损伤, 减少足细胞损伤[86]。除了干细胞本身之外, 研究发现其外泌体也参与了DKD的病理生理过程, 尤其是干细胞衍生的外泌体microRNAs对DKD的潜在治疗作用, 通过激活与mTOR信号通路抑制相关的自噬来预防肾小管上皮细胞凋亡和损伤, 消除间质纤维化, 保护肾足细胞[87]。这种无细胞疗法可以在一定程度上规避活细胞给药相关风险, 因此更具临床转化前景。

虽然干细胞相关疗法为DKD的治疗提供了新的视角, 但其临床转化仍面临诸多的挑战。安全性方面, 移植后的致瘤性风险、细胞的异常分化及潜在的急性免疫反应仍需通过大规模长期随访研究进行系统评估[88]。疗效方面, 注入的干细胞在病变肾脏微环境中的定植效率低、存活时间短及其功能持久性不足, 严重制约了治疗效果的稳定性[89]。此外, 该领域尚未建立统一的标准化体系, 包括细胞来源筛选、体外扩增工艺、输注剂量与途径等关键参数, 这些因素共同构成了临床应用的障碍。因此深入阐释干细胞修复作用的具体分子机制, 特别是其旁分泌效应中起关键作用的活性因子与信号通路网络, 是加速该疗法进入临床的首要任务[90]。同时, 应致力于开发新型递送系统与工程化改造策略, 通过优化制备工艺和增强靶向递送来提高干细胞及其外泌体在肾脏组织的富集度与生物利用度, 并且开展设计严谨的临床试验, 探索干细胞治疗与现有标准疗法 (如SGLT2i) 的协同作用机制, 通过联合治疗策略为DKD患者提供更为安全有效的再生医学解决方案[90]。

3.3 表观遗传调控

前文中提到DKD并非单基因疾病, 其进展与表观遗传调控密切相关。单一对其进行血糖控制, 会使DKD出现“代谢记忆”的现象[91], 即高血糖停止后肾损伤仍持续存在。近些年来的研究表明, 靶向DNA甲基化、组蛋白修饰等表观遗传机制可以有效干预DKD此种“代谢记忆”的现象[92]。*EPHX2*基因甲基化是一种新型生物标志物, 其启动子区CpG位点7的甲基化水平每升高1%, DKD风险增加56%, 而靶向该位点去甲基化可恢复保护性物质EETs的生成, 减轻肾脏损伤[93]。组蛋白修饰可以通过改变染色质的结构影响炎症和纤维化基因表达。外源性γ-氨基丁酸 (GABA) 与经典降糖药二甲双胍具有82.5%的相似度, 作为Sirt1的激活剂, 可以通过降低组蛋白H3的乙酰化水平, 改善糖代谢记忆和肾组织的组织病理学[94]。达格列净可以通过抑制甲基转移酶EZH2, 降低H3K27me3修饰, 甲基化上调ACE2, 通过抑制TGF-β1的下游活化改善肾小管的间质纤维化, 并且EZH2过表达会逆转达格列净的肾脏保护作用, 证明了表观遗传调控的特异性[95]。

表观遗传调控虽然为DKD的治疗提供了一个崭新的维度, 但其临床转化仍面临严峻的挑战。现有表观遗传药物 (组蛋白去乙酰化酶抑制剂或DNA甲基转移酶抑制剂) 普遍缺乏组织特异性, 其在全身给药过程中易引发造血系统异常、胃肠道反应等脱靶毒性[96], 未来的研究应致力于开发肾脏特异性的递送系统, 如利用纳米载体修饰的肾脏靶向配体 (低分子量壳聚糖或特定肽段), 以增强药物在肾组织的富集并降低系统暴露。同时, 须深化对DKD中细胞类型特异性表观遗传图谱的认知, 通过整合单细胞多组学数据, 甄别出驱动疾病进展的核心表观调控节点, 进而设计高选择性抑制剂。在此基础上, 积极探索将表观药物与现有疗法 (如SGLT2i) 的联合策略[97], 或能通过多通路协同干预, 在延缓DKD进展的同时, 实现对肾脏病理重塑的表观遗传重编程, 最终推动其从基础研究向临床治疗的实质性转化。

3.4 中医药治疗

与西药治疗相比, 中医药凭借“多靶点, 整体调节”的优势在改善DKD症状、延缓纤维化和调节代谢紊乱等方面表现出独特的潜力。中医认为DKD属“消渴肾病”“水肿”“虚劳”范畴, 核心病机为“气阴两虚为本, 瘀血、痰浊、湿毒为标”, 因此中医药治疗则以益气养阴、活血化瘀、利湿泄拙为主。越来越多的研究表明, 多种中药及其配伍复方可以延缓DKD的疾病进程, 在疾病治疗中发挥一定的潜力。

中药单体如黄芪甲苷 (AS-IV), 作为黄芪的主要活性成分之一, 可以通过多通路互作网络延缓DKD进展。Li等[98]研究发现在大鼠中, AS-IV可以抑制CD36介导的脂质积累, 阻断NLRP3炎症小体激活, 减轻肾小管间质炎症; 体外实验则表明AS-IV可以通过激活Nrf2-ARE/TFAM信号轴, 减少ROS生成, 抵抗氧化应激诱导的足细胞凋亡及肾损伤[99]; 而在肾小管上皮细胞中, 其可以通过CX3CL1-RAF/MEK/ERK信号级联抑制EMT, 从而延缓DKD纤维化的进程[100]。

近些年的研究证实, 来源于黄连、黄柏等中药的核心活性生物碱——小檗碱 (BBR) 通过多靶点、多通路机制在DKD防治中展现出显著的潜力。Ma等[101]研究发现BBR通过抑制NLRP3炎症小体来抑制高糖诱导的EMT和肾间质纤维化, 抑制NF-κB信号通路的激活可以修复足细胞屏障[102], 还可以阻断促炎因子 (IL-1β、TNF-α) 的上调, 抑制转化生长因子-β/Smad3的信号转导[103], 下调α-SMA、胶原蛋白沉积, 改善肾纤维

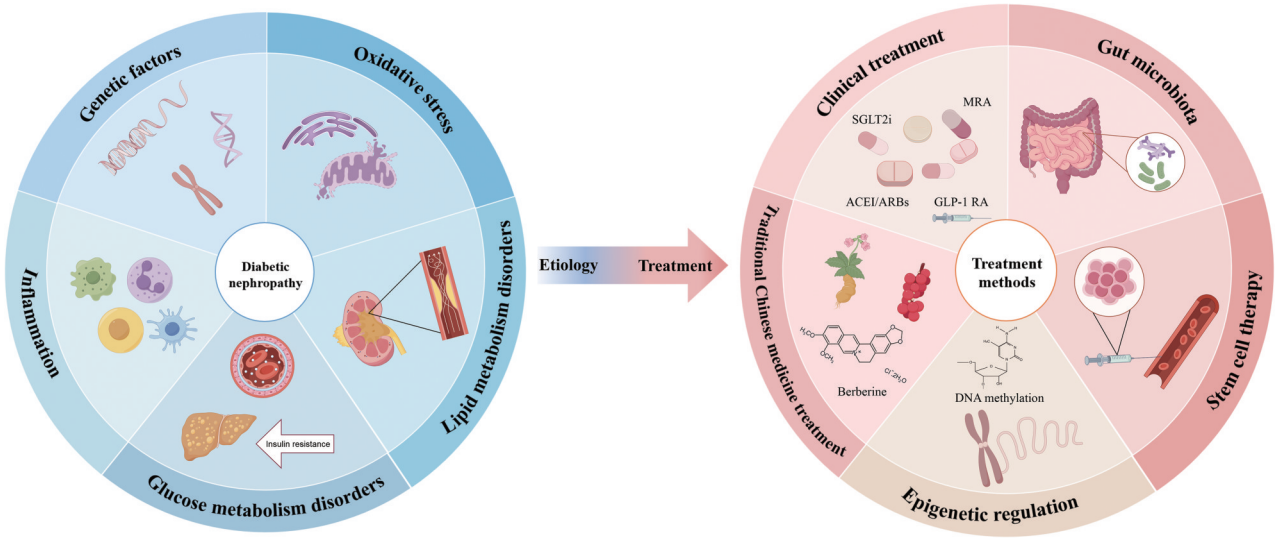


Figure 2 Etiology and treatment strategies for diabetic kidney disease

化。同时 BBR 还可以通过 Nrf2-GPX4 轴阻断肾小管上皮细胞铁死亡, 抑制在 DKD 疾病进展中的氧化应激, 铁死亡诱导剂 erastin 可逆转 BBR 的肾脏保护作用[104]。

中医药还注重阴阳调和、配伍使用。传统复方如济生肾气丸、糖肾方等经过多年临床校验, 已经成为治疗 DKD 等多种肾脏疾病的常用方剂。已有研究表明, 济生肾气丸可以通过调节 AGE/RAGE 轴和 PI3K/AKT 信号通路改善 DKD 小鼠肾脏炎症和细胞凋亡, 减少 DKD 肾损伤[105]。金匮肾气丸是一种用于缓解尿频和多尿等泌尿系统疾病的传统中药配方, 其与二甲双胍联用可通过下调免疫复合物 MHC II 类分子、减弱 MHC II 类对 CD4 的抗原呈递作用, 减轻 DKD 的肾纤维化[106]。以上研究提示, 中医药在治疗 DKD 方面具有较高的可行性, 但仍需注意, 相较于现代药物大规模、随机、双盲、安慰剂对照的临床试验, 中医药研究多为小样本、单中心观察性研究, 其结论易受偏倚影响[107]。此外, 中药复方成分复杂, 其药效物质基础、体内代谢过程及多组分协同作用机制尚未完全阐明, 加之药材来源与制剂工艺的标准化难题, 共同导致了疗效的异质性与可重复性不佳。

尽管中医药治疗 DKD 的高级别循证证据尚显不足, 但在临床实践中, 基于其多成分、多靶点的治疗特性与现代化药理研究的初步验证, 中西医结合的疗法已展现出独特的应用价值。

4 总结与展望

DKD 的病因与治疗策略如图 2 所示。随着对 DKD 发病机制的深入研究, DKD 的防治正经历从症状管理到机制干预的深刻转型。尽管以 SGLT2i 为代表的现代疗法在延缓疾病进程方面成效显著, 但其难以逆转已形成的组织结构损伤, 未来的治疗突破将不再依赖于单一靶点的发现, 而在于实现治疗理念的范式革新[108]。研究的下一步应致力于从孤立通路的干预转向对病理网络的系统性调控。DKD 的病理本质是代谢紊乱–炎症反应–纤维化进程的连续损伤过程, 探索能够同时协调多个核心环节的关键节点, 如旨在协同纠正胆固醇代谢紊乱与抑制炎症反应的联合策略, 或利用干细胞及其外泌体对损伤微环境进行功能性重塑, 将成为实现疾病修饰性治疗的关键。临床转化的瓶颈则需要前沿技术与精准医疗的深度融合, 开发肾脏特异性的递送系统[109]。与此同时, 面对患者显著的个体异质性, 未来研究需通过整合多组学数据构建可指导临床决策的生物标志物体系[110], 从而实现对不同亚型患者的精准分层与靶向干预。此外, 中西医结合的深化实践提供了独特视角。其价值实现路径在于超越传统经验, 运用现代科学方法阐释中药复方在多靶点调控中的协同逻辑, 并将其机制明确地整合进现代诊疗框架, 形成优势互补的治疗方案。

总之, DKD 的防治任重而道远, 需要科研与临床的紧密协作。未来, 随着对发病机制的进一步阐明以及新的治疗方法和药物的不断涌现, DKD 治疗将取得更大的突破, 为患者带来新的希望。

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