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糖代谢重塑与慢性肾脏病

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摘要：慢性肾脏病(chronic kidney disease，CKD)是由多种原因造成的肾脏结构或功能持续性损伤的疾病，常伴随着糖代谢异常。肾脏糖代谢稳态失衡，尤其是糖酵解速率加快，会造成细胞应激性损伤，引发肾脏细胞衰老、炎性细胞因子的分泌和细胞外基质堆积。鉴于此，深入解析肾脏糖代谢调控机制并筛选触发糖代谢重塑的分子靶点对于CKD的防治至关重要。本文概述了肾脏糖代谢稳态失衡的关键因素及其导致细胞损伤的机制；归纳总结了糖代谢异常在CKD慢性肾脏病过程中的肾脏炎症、肾脏衰老和肾纤维化的影响；最后介绍了糖代谢重塑在CKD慢性肾脏病发生发展中的作用。本综述对糖代谢重塑和CKD内在关联的深入探讨，有望为肾脏疾病的治疗提供科学依据。

关键词：慢性肾脏病；糖代谢；细胞损伤；代谢重塑

Remodeling of glucose metabolism and chronic kidney disease

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Abstract: Chronic kidney disease (CKD) is characterized by persistent impairment of renal structure or function, resulting from various causes and often accompanied by disruptions in glucose metabolism.

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Dysregulation of renal glucose metabolism, particularly the acceleration of glycolysis, may induce cellular stress and injury, leading to cellular senescence, inflammation, and the accumulation of extracellular matrix. Understanding the regulatory mechanisms governing renal glucose metabolism and identifying molecular targets for its remodeling are crucial for prevention and treatment of CKD. This review highlights key factors contributing to renal glucose homeostasis imbalance and the mechanisms through which they cause cellular damage. It also summarizes the impact of abnormal glucose metabolism on renal inflammation, aging, and fibrosis during CKD progression. Additionally, the review introduces the potential roles of glucose metabolism remodeling in CKD development. This comprehensive exploration of the relationship between glucose metabolism remodeling and CKD aims to provide theoretical foundation for kidney disease treatment.

Key Words：chronic kidney disease; glucose metabolism; cellular injury; metabolic remodeling

慢性肾脏病(chronic kidney disease，CKD)是一种以肾小球滤过率持续下降为显著特征的临床综合征，表现为肾脏结构和功能的渐进性、持续性损伤[1]。据统计，CKD在全球范围的发病率约为10%，在过去几十年，其死亡率显著上升，预计2040年将成为全球第五大致死病因[2]。随着生活水平的提高和饮食结构的改变，大量高热量食品摄入体内，导致CKD患者呈现年轻化的趋势，其中20岁男性CKD 3-5期的患病率为4.7%，女性患病率则升高到5.8%[3,4]。若病情进一步恶化，CKD患者最终发展为终末期肾病，需要通过透析或肾移植来维持生命[5]。CKD还会带来一系列并发症，包括心血管疾病和代谢性疾病等，给社会和家庭带来沉重的经济负担[6]。流行病学研究表明，高血糖引起的代谢紊乱是导致糖尿病肾病(diabetic nephropathy，DN)的主要诱因，也是CKD进展至终末期肾病乃至最终死亡的重要原因[5,7]。高水平的葡萄糖与活性氧(reactive oxygen species，ROS)和晚期糖基化终产物(advanced glycation end products，AGEs)的产生直接相关，可引起肾脏炎症和氧化应激，加快CKD进程[8,9]。鉴于葡萄糖稳态失衡与肾脏疾病密切相关，越来越多的研究聚焦于糖代谢对CKD发生发展的影响。本文将综合阐述糖代谢失衡在CKD发生发展中的作用和调控机制，并对基于糖代谢重塑改善CKD的潜在靶点和策略进行了综述。

1 肾脏糖代谢稳态失衡的因素及与细胞损伤的关系

1.1 高糖引起糖代谢失衡

葡萄糖是机体维持正常生理功能的主要能量来源之一。肾脏在维持机体葡萄糖稳态中扮演着重要角色，其主要通过三种途径发挥调节作用：从血液循环中摄取葡萄糖，肾小球滤液中重新吸收葡萄糖以及通过糖异生作用将非糖物质转化为葡萄糖并释放到循环中[10]。肾脏消耗的葡萄糖大约占机体利用葡萄糖的10%[11]。肾脏不同区域对葡萄糖的利用存在差异，其中肾髓质对葡萄糖进行摄取利用，而肾皮质几乎不摄取和利用葡萄糖[10]。正常情况下，葡萄糖可以经肾小球自由滤过，并且随着血浆葡萄糖水平的升高，肾小球过滤液中的葡萄糖量呈线性增加。当血浆葡萄糖浓度超过肾糖阈(180 mg/100 mL)时，超出的葡萄糖量将被排出体外[12]。和肝脏类似，肾脏也被认为是糖异生的主要场所，特别是在吸收后阶段(营养物质被完全吸收，机体依靠糖异升产生葡萄糖)和长期饥饿情况下，肾脏糖异生对机体血糖的贡献可达40%~50%[13]。肾脏糖代谢三种途径协同运行，共同调节肾脏和机体的糖代谢稳态。

在高血糖条件下，葡萄糖代谢通量从线粒体的有氧氧化转移到糖酵解途径。DN小鼠肾脏和尿液中的糖酵解代谢产物的增加以及肾外髓质中的葡萄糖6-磷酸和甘油醛3-磷酸水平的显著升高证实了进入糖酵解途径和磷酸戊糖途径的葡萄糖代谢通量增加[14]。有研究发现，肾小管细胞代谢的改变会增加成纤维细胞的糖酵解能力，为成纤维细胞增殖和活化提供能量[15]。糖酵解的产物丙酮酸继续氧化生成乙酰辅酶A，进入三羧酸循环，引起循环中代谢物如柠檬酸、苹果酸、琥珀酸等水平升高[16]。三羧酸循环代谢物累积引起的线粒体功能障碍，是DN早期肾损害的潜在指标和DN并发症发

生的重要因素[14,17]。肾脏被认为是体内主要的乳酸库，在乳酸清除中发挥重要作用[18]。乳酸既是糖酵解的产物，也是糖异生的重要原料。当肾脏糖酵解速率增加或者糖异生途径受到阻碍引起乳酸生成增加或者清除减少时，乳酸会在局部堆积，造成酸性微环境，进而激活肌成纤维细胞，促进肾纤维化[19,20]。

1.2 糖代谢异常造成肾脏细胞压力性损伤

高糖引起肾脏多个糖代谢途径失调，促进有害代谢物累积，从而造成肾脏细胞的压力性损伤(图1)。高糖诱导ROS过量产生、加剧细胞氧化应激和线粒体损伤的主要途径是：多元醇途径和己糖胺途径增强、AGEs的形成以及蛋白激酶C(protein kinase C，PKC)的激活[21,22]。多余的葡萄糖可经多元醇途径还原成山梨糖醇并将还原型烟酰胺腺嘌呤二核苷酸磷酸(nicotinamide adenine dinucleotide phosphate，NADPH)氧化为$NADP^+$，降低细胞的抗氧化能力，导致线粒体ROS的产生增多[23]。高糖还会引起己糖胺途径增强，抑制胰岛素信号，影响线粒体的形态、大小和数量，引起线粒体功能障碍[24,25]。糖酵解速率增加导致甲基乙二醛大量产生，并与蛋白质的赖氨酸、精氨酸和半胱氨酸残基反应，形成不可逆的AGEs[26]。这些AGEs在血液循环和组织中积累，与内皮细胞表面的受体结合后会诱导ROS产生、线粒体损伤和内质网应激[27,28]。肾小球内皮细胞产生的一氧化氮对足细胞具有保护作用，AGEs则通过减少内皮型一氧化氮合酶表达使一氧化氮失活，加剧足细胞的损伤[29,30]。高糖还会促进PKC激活，增加ROS产生和线粒体DNA损伤[31]。过多的糖酵解产物可以直接激活内质网应激相关蛋白，诱导肾脏细胞出现强烈的内质网应激[32]。糖代谢途径异常导致氧化应激，线粒体功能障碍和内质网应激等会加重细胞损伤，进而加速DN和CKD的进展。

肾脏中主要发挥功能的是肾小管上皮细胞、肾小球内皮细胞、足细胞和系膜细胞[33]。糖酵解速率增加会导致肾小球内皮细胞功能障碍并促进肾小球内皮细胞凋亡，破坏肾小球滤过屏障[34]。研究表明，PKC参与介导了糖代谢异常引起的肾小球内皮细胞高通透性[35]。PKC的激活上调内皮细胞中的环加氧酶-2水平，导致肾脏血流动力学变化，并增强血管内皮生长因子和转化生长因子-β(transforming growth factor-β，TGF-β)信号，促进内皮损伤并加快肾小球病变，抑制PKC-β可以减少尿白蛋白并减轻肾小球和肾小管间质损伤[36-38]。糖代谢异常可能引起足细胞形态和功能的改变，包括肥大、足突消失、上皮-间质转化(epithelial-mesenchymal transition，EMT)和凋亡等[39]。研究表明，TGF-β和哺乳动物雷帕霉素靶蛋白C(mammalian target of rapamycin complex，mTORC)的表达上调与足细胞

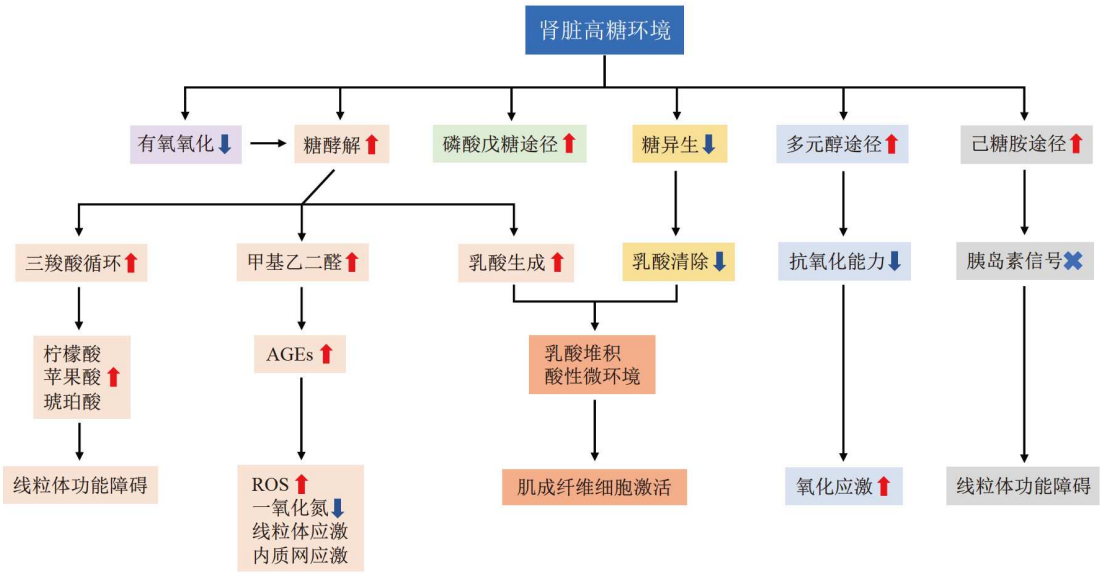

图1 高糖环境引起的糖代谢异常加快肾细胞损伤

糖代谢紊乱、足细胞肥大和足突消失密切相关[40]。足细胞的EMT是发生蛋白尿的潜在途径，糖代谢紊乱激活多条信号通路导致足细胞发生EMT，进而损伤肾小球滤过功能[41,42]。自噬则可以保护足细胞免受糖代谢紊乱诱发的损伤，然而长期的高糖环境以及糖酵解水平过高会下调自噬水平，促进足细胞损伤[43,44]。在糖尿病动物模型中，高血糖引起沉默信息调节因子1(silent information regulator 1，SIRT1)的表达降低，导致自噬减少和线粒体功能障碍，进而诱导足细胞损伤[45]。在糖尿病小鼠模型和糖尿病患者的足细胞中，mTOR的上调与足细胞自噬的抑制有关，损害足细胞功能[46,47]。系膜扩张被认为是肾脏疾病进展到晚期阶段的标志之一，糖代谢异常引起系膜细胞中平滑肌肌动蛋白的增多，导致系膜扩张和肾小球硬化[48]。肿瘤坏死因子-α(tumor necrosis factor-α，TNF-α)和结缔组织生长因子的增加共同促进肾小球硬化，加速CKD的发展[49]。

2 糖代谢紊乱对慢性肾脏病的影响

糖代谢异常诱发的肾脏内皮细胞、足细胞和系膜细胞损伤逐步造成肾脏组织结构的破坏以及肾脏功能的缺失，这一过程往往涉及肾脏炎症、肾纤维化以及肾脏衰老(图2)。

2.1 糖代谢紊乱与肾脏炎症

炎症反应是肾损伤的驱动因素，与DN和CKD的发生发展密切相关[50]。葡萄糖及其代谢产物乳酸和琥珀酸等在炎症过程中扮演着重要角色[51]。肾脏糖代谢失调激活核转录因子κB(nuclear factor kappa B，NF-κB)和TGF-β在内的通路，引发炎性细胞因子和炎症标志物如TNF-α和白介素-1β(interleukin-1β，IL-1β)的表达增加[52,53]。在DN模型中，糖代谢紊乱激活PKC-β引起的NF-κB信号增强，导致炎性细胞因子的大量释放[54]。NF-κB被认为是调控各种炎性介质基因表达的“总开关”，抑制NF-κB的活性可以降低靶基因的表达，减少炎症反应，从而改善肾损伤和纤维化[55,56]。阻断mTOR信号传导能够降低细胞糖酵解水平，抑制TGF-β1诱导的成纤维细胞活化，减轻肾间质炎症和纤维化[57,58]。TNF-α在炎症过程中具有多方面的作用，包括影响白细胞的募集和激活，介导糖代谢紊乱对足细胞、系膜细胞和内皮细胞的毒性作用[59,60]。IL-1β主要由巨噬细胞产生，触发肾脏细胞产生次级促炎介质[61]。抗IL-1β抗体治疗可以减少糖尿病小鼠的肾纤维化、足细胞损伤并减缓肾小球滤过率的进行性下降[62]。糖酵解增加引起的慢性低度炎症还会导致胰岛素抵抗，进一步加剧CKD的进展[63]。

2.2 糖代谢紊乱与肾纤维化

肾纤维化是CKD的一个基本病理变化，其特征包括致纤维化细胞因子分泌增多、肌成纤维细胞活性增加以及炎症反应，最终导致肾小球硬化、肾间质纤维化和肾功能丧失[64]。肌成纤维细胞的过度增殖是纤维化的标志之一。研究显示，从线粒体氧化磷酸化到糖酵解的代谢转变是肌成纤维细胞活化的主要特征，利用抑制剂破坏糖酵解途径，可以显著抑制肾纤维化和肾小管细胞凋亡[65]。研究发现，TGF-β与多种疾病和实验模型中的组织纤维化的发病密切相关。糖代谢紊乱则会引起系膜细胞中TGF-β等促纤维化因子的表达上调[66]。糖酵解速率增加导致三羧酸循环中的琥珀酸水平升高，琥珀酸的增加会进一步上调TGF-β1和IL-1β的表达[67]。葡萄糖还能诱导细胞表面TGF-β受体的快

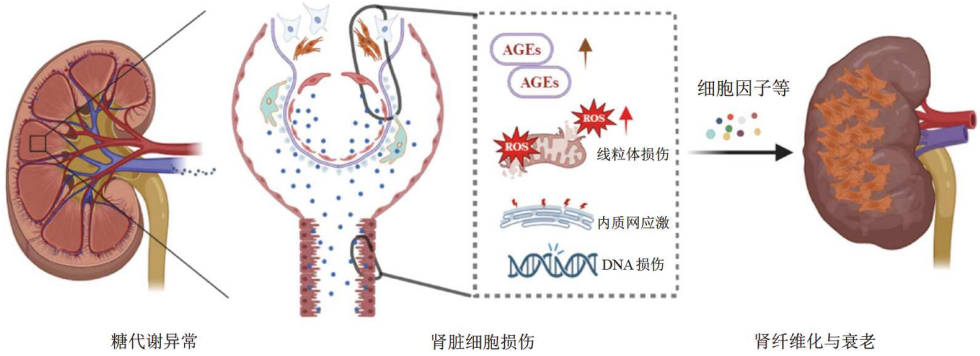

图2 糖代谢紊乱与慢性肾脏病的内在联系

速外化，加速纤维化相关的TGF-β信号通路传导[68]。研究发现，高糖处理的肾小球内皮细胞分泌含有TGF-β1 mRNA的外泌体，这些外泌体能够诱导系膜细胞和足细胞发生EMT和滤过功能障碍[69,70]。核因子E2相关因子2(nuclear factor erythroid 2 related factor 2，NRF2)激活剂能够改善葡萄糖稳态和氧化应激状态[71]，*NRF2*敲除的糖尿病小鼠表现出更明显的炎症和氧化应激增加，肾小球硬化加重以及纤维化标志物水平升高[72]。天然NRF2激活剂如姜黄素已被证实能有效地减轻CKD动物实验模型中的炎症、氧化应激和肾纤维化[73]。白藜芦醇能通过增强腺苷酸激活蛋白激酶(AMP-activated protein kinase，AMPK)活性，减轻高糖诱导的肾成纤维细胞增殖和活化，减缓肾纤维化的进程[74]。这些发现证实了糖代谢异常在肾纤维化中起着重要作用，改善糖代谢异常和抑制糖酵解的药物可能是控制肾纤维化进展的有效策略。

2.3 糖代谢紊乱与肾脏衰老

肾小管上皮细胞、肾小球内皮细胞、系膜细胞和足细胞的衰老与肾脏疾病的进展具有高度的相关性[75,76]。糖代谢异常引起的炎症、氧化应激、AGEs的积累以及DNA损伤等都是推动肾脏细胞衰老的关键因素[77,78]。葡萄糖的大量内流提高细胞的糖酵解速率并激活mTOR信号通路，通过上调p16和p21蛋白的表达水平，诱导巨噬细胞分泌衰老相关分泌表型(senescence-associated secretory phenotype，SASP)来引起炎症反应，加速肾脏衰老过程[79,80]。TGF-β作为SASP因子之一，已被证实能够诱导各种细胞类型的衰老[81]。研究发现，AGEs诱导的足细胞损伤和系膜细胞凋亡会导致肾功能发生障碍并加速肾脏衰老，抑制其活性则可以减轻糖代谢失调诱导的肾小管上皮细胞早衰[82,83]。糖代谢异常引起的氧化应激和AGEs积累会导致DNA损伤，进一步诱发肾小球和肾小管细胞的持续性损伤和早衰[80,84]。此外，糖代谢紊乱能够加快肾小管上皮细胞中染色体端粒的缩短，这与肾脏细胞衰老、蛋白尿以及DN的进展密切相关[85]。糖酵解的增强不仅能加速快线粒体功能障碍，还会导致SIRT1的表达下调，对肾脏过早衰老起到推波助澜的作用[86]。AMPK可通过增加细胞内烟酰胺腺嘌呤二核苷酸(nicotinamide adenine dinucleotide，NAD^+)的水平来增加SIRT1活性，增强自噬和修复DNA损伤，减轻肾损伤并有助于延缓衰老[87,88]。白藜芦醇处理也会增加SIRT1表达，抑制糖酵解，调节葡萄糖稳态，从而起到保护肾脏的效果[89,90]。这些研究提示，改善糖代谢紊乱有助于延缓肾脏衰老。

3 糖代谢重塑在慢性肾脏病发生发展中的作用

鉴于糖代谢异常是驱动CKD发生发展的关键因素，通过控制饮食、加强锻炼以及采用新的药物治疗策略有效控制糖代谢稳态，深入解析肾脏糖代谢调控及其引发肾损伤的机制，筛选触发糖代谢重塑的分子靶点，对于减轻肾脏疾病至关重要。

3.1 饮食干预引起的糖代谢改变

鉴于糖代谢稳态失衡在CKD的发病机制和病程进展中发挥关键作用，合理的饮食控制，尤其是减少糖分摄入，对于延缓CKD的进展具有重要意义。世界卫生组织制定的指南建议将游离糖的摄入量限制在总能量摄入的10%以内，并尽可能降低至5%[91]。医学研究主张将每日糖摄入量的最大阈值设定为总热量消耗的25%[91]。为了有效控制血糖并减轻CKD患者的肾损伤，研究者建议增加富含类黄酮的水果和蔬菜摄入，如绿叶蔬菜、水果、豆类和浆果等，补充膳食纤维和益生菌，减少单糖的消化和吸收，对改善炎症和氧化应激具有积极影响[92,93]。高糖饮食与多种健康风险相关，维生素E作为一种有效的抗氧化剂，能够降低氧化应激和炎症水平[94]。此外，维生素D具有调节血糖、抗氧化、抗炎、抗血管生成和抗衰老等作用，在血流中维持足够的维生素D水平，有助于减轻高血糖对微血管系统的不良影响[95,96]。尽管带来降血糖效应，饮食干预调控肾脏糖代谢的报道并不多。一项小鼠肾脏的RNAseq显示，含0.2%腺嘌呤的饲料喂食的小鼠肾脏中糖异生相关基因表达降低，并伴随肾脏氧化压力、炎症和纤维化的增加[97]。最近研究发现，高脂饮食喂养的小鼠肾脏中糖异生的关键酶——磷酸烯醇丙酮酸羧激酶1和葡萄糖-6-磷酸酶的基因表达水平升高[98]。这些研究显示，不同的饮食对肾脏糖代谢的影响并不同，提示进行饮食干预降低血糖的同时需要考虑到肾脏糖代谢的变化，这样更有利于CKD的防治。

3.2 运动引起的糖代谢重塑

坚持进行运动锻炼可降低糖化血红蛋白水平，改善葡萄糖调节能力，并防止胰岛素抵抗的发生[99,100]。适量有氧运动还能够增强机体的抗氧化系统，提高体内超氧化物歧化酶、谷胱甘肽等抗氧化剂的活性，减少氧化应激对机体的损害[101]。保持适量的有氧运动能够减少炎症标志物的水平，改善线粒体功能障碍，防止DNA损伤[102,103]。有研究报道，端粒长度是生物衰老的一个指标，坚持有氧运动对预防端粒磨损和改善端粒长度具有积极作用[103]。

3.3 药物治疗引起的糖代谢重塑

在CKD患者中，由于胰岛素抵抗和高血糖的存在，糖酵解途径被过度激活，导致代谢产物积累和氧化应激增加，加剧肾脏的代谢负担。因此，在CKD患者的综合治疗中，血糖控制和干预糖酵解途径是至关重要的一环，有助于降低终末期肾病的发生风险[104]。

3.3.1 SGLT-2抑制剂

钠-葡萄糖协同转运蛋白-2(sodium-dependent glucose transporters-2，SGLT-2)主要分布在肾脏近端小管，负责滤液中约90%葡萄糖的重吸收[105]。研究表明，SGLT-2抑制剂通过阻碍肾脏对葡萄糖重吸收，增加葡萄糖糖排泄，从而有效降低血糖水平[106]。SGLT-2抑制剂具有肾脏保护作用，这与其降低肾脏的高滤过状态、减轻炎症和氧化应激的效用有关[105]。抑制SGLT-2可以阻断葡萄糖摄取，降低细胞内的糖酵解水平，有利于抑制近端小管细胞EMT[106]。SGLT-2的一种抑制剂——恩格列净可以减轻糖尿病动物模型的肾小球超滤状态，减少炎症和氧化应激[107]。其他SGLT-2抑制剂的相关研究也显示出了类似的抗炎和抗氧化作用[108]。2型糖尿病患者经恩格列净治疗后，肾功能得到明显改善，CKD发生率也有所降低，进一步证实SGLT-2是基于糖代谢防治CKD的有效分子靶点[109]。

3.3.2 GLP-1受体激动剂

胰高血糖素样肽-1(glucagon-like peptide-1，GLP-1)是由肠道细胞合成和分泌的一种肠促胰岛素激素，在调节血糖方面发挥重要作用。GLP-1受体激动剂是一类新型降糖药物，能够显著降低空腹血糖、餐后血糖和糖化血红蛋白水平[110]。GLP-1受体激动剂具有改善肾脏结构和功能的潜力。研究表明，GLP-1受体激动剂可以改善糖尿病大鼠的蛋白尿、肾小球肥大和基质扩张，同时减少炎症和纤维化相关标记物的表达[110,111]。服用GLP-1受体激动剂艾塞那肽治疗后，2型糖尿病患者尿白蛋白、尿TGF-β1和Ⅳ型胶原的排泄即明显减少，表明GLP-1受体激动剂能够减轻肾脏的炎症和纤维化[112]。另一种GLP-1受体激动剂利拉鲁肽在临床试验中显示出了减轻患者炎症和氧化应激的作用[113]。

3.3.3 中草药

近年来，中草药在肾脏疾病治疗领域的研究取得了显著进展。一系列中草药活性成分，如黄芪皂苷和小檗碱等被证实在调节葡萄糖代谢、抗炎、抗氧化、抗纤维化以及保护足细胞等方面发挥重要作用，这些成分通过多种作用机制，在CKD的治疗中显示出了良好的临床效益[114]。

黄芪皂苷是黄芪的活性成分之一，已在多项研究中显示出对肾脏疾病的潜在治疗价值，它不仅可以改善肾损伤，减少尿白蛋白排泄，还能有效抵抗足细胞足突消失[115]。研究表明，黄芪皂苷能够有效降低血糖水平，减轻肾脏的高滤过状态；还能阻断NF-κB信号通路，降低促炎细胞因子IL-1β、IL-6和TNF-α的表达，有效抑制炎症反应，减轻肾脏损伤[116,117]。此外，黄芪皂苷还能降低TGF-β水平，改善足细胞的去分化状态和系膜细胞的过度增生[118]。Klotho蛋白主要在肾脏中表达，被认为是一种有前途的抗氧化和抗衰老调节剂，黄芪皂苷通过上调Klotho的表达，增强足细胞的抗氧化能力，抑制足细胞凋亡，对CKD具有显著的保护性作用[119,120]。

小檗碱是从黄连中提取的一种生物碱，能够调节糖酵解途径，具有显著的降血糖效果，在维持血糖稳态中发挥重要作用；同时，还显示出良好的肾保护作用[121]。在体内实验中，小檗碱能够阻断NF-κB等炎症相关信号通路，减少促炎细胞因子的产生[122]。临床研究结果进一步证实了小檗碱的抗炎作用，治疗后血浆中促炎细胞因子水平呈显著下降趋势[123]。此外，小檗碱还能显著减少AGEs的产生，降低TGF-β1的表达，从而延缓肾间质纤

维化的进展[124]。小檗碱已被证实能够增加超氧化物歧化酶活性，并上调抗氧化基因的表达，减轻细胞的氧化应激和保护线粒体功能[123,125]。

4 总结

糖代谢稳态失衡是导致DN发生，加速CKD发展的主要原因之一。血糖水平的持续升高导致肾脏糖酵解水平的增加，以及其他代谢途径的异常激活，这些变化会引发炎症细胞因子和ROS的产生增加，引起慢性炎症、氧化应激、内质网应激、线粒体功能障碍等，从而进一步加剧肾损伤、肾纤维化和肾脏细胞衰老。干预肾脏的糖代谢紊乱，促进糖代谢重塑，维持正常的血糖水平和葡萄糖稳态，对于减轻肾损伤和延缓CKD的进展具有重要意义。深入研究糖代谢重编程的分子机制，寻找更多有效的潜在治疗靶点，会为CKD的防治和临床药物开发提供有价值的参考。

作者贡献声明：

秦炜宏：设计论文框架，起草论文，论文修改，资料查询，绘制示意图；

杨　萌：设计论文框架，论文修改；

刘新光：拟定写作思路，指导撰写文章并定稿。

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