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SGLT–2 抑制剂对糖尿病肾病的保护作用的研究进展

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[摘 要] 糖尿病肾病(diabetic nephropathy，DN)是糖尿病严重的并发症之一，部分患者会进展为终末期肾病(end-stage renal disease，ESRD)，病死率明显高于不伴肾病的糖尿病患者。钠-葡萄糖转运蛋白2(sodium-glucose transporter 2，SGLT-2)抑制剂是一种新型降糖药物，目前研究发现，除降糖作用外还有减轻体重、改善血压、减少尿蛋白、降低血尿酸、改善肾小球超滤和氧化应激、抑制炎症和纤维化等作用，可以通过多种途径保护肾脏，有望用于预防及延缓DN的发生和发展。未来可以进一步探索SGLT-2抑制剂的肾保护机制，亦可以基于其肾保护作用扩展应用于非DN患者。

[关键词] 钠-葡萄糖协同转运蛋白2抑制剂；糖尿病肾病；保护作用

Research progress on the protective effect of SGLT-2 inhibitors on diabetic nephropathy

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Abstract Diabetic nephropathy (DN) is one of the serious complications of diabetes. Some patients will progress to end-stage renal disease (ESRD), and the mortality rate is significantly higher than that of diabetics without DN. Developed originally as glucose-lowering drugs by enhancing urinary glucose excretion, sodium-glucose transporter 2 (SGLT-2) inhibitors also lower many other renal risk factors such as body weight, blood pressure, albuminuria, uric acid and improve renal oxygenation, intra-renal inflammation thereby slowing the progression of kidney function decline. Future research can explore the mechanism of SGLT-2 inhibitors' protective effect on kidney, and its potential in the treatment of non-diabetic kidney disease.

Keywords sodium-glucose transporter 2 inhibitors; diabetic nephropathy; protective effect

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2型糖尿病是严重的公共卫生疾病之一，在全球普通人群中的患病率为10%，2013年影响了超过4.15亿成年人，预计到2035年，这一数字将增加到5.92亿[1-2]。大约40%的糖尿病患者会发展为糖尿病肾病(diabetic nephropathy，DN)，这些患者中又有一部分会进展为终末期肾病(end-stage renal disease，ESRD)[3]。最近的研究[4]表明，DN患者的10年病死率较不伴肾脏病的糖尿病患者显著增加。因此，研发新的治疗方法以预防及延缓DN的发生和发展是非常必要的。目前糖尿病患者肾脏以及心血管并发症的防治重点是控制血糖、血压、体重、尿蛋白和尿酸等危险因素，降低心血管和肾功能进一步损害的风险[5]。钠-葡萄糖协同转运蛋白2(sodium-glucose transporter 2，SGLT-2)抑制剂是一种新型降糖药物。SGLT-2抑制剂除降糖作用外，还有降低血压、减轻体重、降低血尿酸、改善肾小球高滤过、减少蛋白尿、改善氧化应激、抑制炎症和纤维化等作用[6-16]。本文综述了SGLT-2抑制剂潜在肾脏保护作用的最新研究进展，并展望了SGLT-2抑制剂在非糖尿病肾病患者中的应用前景。

1 SGLT-2 抑制剂的降糖机制

在健康的人群中，每天有约180 g葡萄糖由肾脏滤过，在近曲小管SGLT的作用下，尿糖几乎完全被重吸收[17]。SGLT主要有SGLT-1和SGLT-2两种类型，位于近曲小管近端上皮细胞的SGLT-2，是一个高容量、低亲和力的转运蛋白，它负责大约90%的尿糖的重吸收，剩余的10%由位于近曲小管远侧段的低容量、高亲和力的SGLT-1转运蛋白重吸收[18]。

在糖尿病患者中，SGLT-2的表达上调，尿糖排泄的阈值增加[19]。SGLT-2抑制剂可特异性抑制肾小管对葡萄糖的重吸收，从而增加尿糖的排泄，其降糖作用与胰岛素的分泌无关[20]。有研究[21]表明，SGLT2抑制剂的降糖作用与肾小球滤过率(estimated glomerular filtration rate，eGFR)呈依赖关系。在肾功能正常的人群中可以使糖化血红蛋白降低0.97%，而在肾小球滤过率在30~59 mL/(min·1.73 m^2)的人群中，可使糖化血红蛋白降低0.3%~0.4%，在eGFR <30 mL/(min·1.73 m^2) 的人群中无明显改善糖化血红蛋白的作用[21]。

2 SGLT-2 抑制剂的肾脏保护机制

2.1 改善肾脏血流动力学

肾小球高滤过状态是慢性肾脏病(chronic kidney disease，CKD)的早期临床表现之一，是由糖尿病引起的肾结构和激素水平的变化相互作用的结果[22]。肾小球高滤过状态是微量白蛋白尿和进行性肾功能下降的高风险因素[22]。在非糖尿病状态下，SGLT-2负责大约5%的钠的重吸收，在高血糖的情况下，SGLT-2和SGLT-1的mRNA表达增加约36%和20%，运输到致密斑的钠减少导致球管反馈抑制，从而引起入球小动脉扩张、肾血流量增加和肾小球高滤过[6-7]。SGLT-2抑制剂可抑制肾近端小管对钠的重吸收，增加远端钠输送，从而恢复球管反馈和改善肾小球高滤过[23]。

2.2 改善氧化应激，抑制炎症和纤维化

炎症、氧化应激和纤维化都参与了肾脏疾病的发生和发展[24-25]。实验研究[8-10]已经证明SGLT-2抑制剂与抗炎、抗氧化和抗纤维化标志物的减少有关。一项研究表明在使用伊格列净和恩格列净治疗后，单核细胞趋化因子-1(monocyte chemoattractant protein-1，MCP-1)，核转录因子(nuclear factor kappa B，NF-kB)，8-羟基脱氧鸟苷(8-hydroxy-2'-deoxyguanosine，8-OHdG)和L-脂肪酸结合蛋白(liver-type fatty acid-binding protein，L-FABP)等氧化应激和巨噬细胞标志物的水平降低[8-9]。另有一项研究[10]表明：与安慰剂相比，使用达格列净治疗6周后尿中炎性标志物白介素-6(interleukin 6，IL-6)降低23.5%，MCP-1降低14.1%。肾脏近端小管负责大部分的水、有机溶质和电解质的重吸收，这些过程是氧依赖性的，SGLT-2抑制剂减少钠和葡萄糖的重吸收，可减轻肾小管负荷，减少其缺氧，从而减少肾小管损伤，改善肾小管细胞的结构和功能[26]。

2.3 改善血压

Logistic回归分析表明收缩压是尿蛋白进展的独立危险因素[27]。收缩压为140~149 mmHg (1 mmHg=0.133 kPa)的患者进展为ESRD的风险增加，收缩压>150 mmHg的CKD患者进展为ESRD的风险增加一倍以上[28]。因此，控制血压有利于延缓CKD的发展。在EMPA-REG结果试验中，与安慰剂组相比，恩格列净组的收缩压下降4 mmHg，且在较低的eGFR水平下，SGLT-2抑制剂的降压作用不会减弱[11]。在一项为期24周的达格列净的试验中同样观察到，在eGFR基线水平不同的各个分组中降压效果是一致的[12]。SGLT-2抑制剂的降压作用可能与改善动脉顺应性有关[29]。在CKD患者中，血压难以达到最佳控制是导致动脉硬化的一

个关键因素，脉搏波传导速度是一项测定动脉硬化的指标[29]。已有研究证明在接受恩格列净治疗后脉搏波传导速度显著降低，这可能是是由于体重减轻或负钠平衡，使血管平滑肌松弛，除此之外，也可能与SGLT-2抑制剂对氧化应激和内皮功能障碍的改善有关[29-30]。

2.4 减轻体重

一项横断面研究[31]表明，肥胖是糖尿病患者发生微量白蛋白尿的重要危险因素。除此之外，有研究[32-33]认为肥胖通过影响肾小球滤过、脂肪因子及引起慢性炎症、肾素-血管紧张素-醛固酮系统紊乱而影响肾功能。在EMPA-REG试验结果中显示，与安慰剂相比，10 mg/d或25 mg/d的恩格列净可使体重下降约2 kg[11]。在CANVAS和CANVAS-R实验结果中观察到，与安慰剂相比，100 mg/d或300 mg/d的卡格列净组体重都有明显的减少[13]。这可能与SGLT-2抑制剂引起的尿糖增加带来的热量损失有关，同时也间接导致了代谢增加、脂肪分解[13]。在另一项研究中观察到，在开始服用恩格列净的2周内血浆甘油、脂肪酸水平的增加(反映加速脂肪分解)和β-羟基丁酸酯水平升高(反映加速肝脏脂肪氧化)[34]，这些效应共同作用导致了体重的减轻。

2.5 减少尿蛋白

在EMPA-REG结果试验中，与安慰剂组的16.2%相比，恩格列净组有11.2%的患者进展为大量蛋白尿，相对减少38%，恩格列净组大量蛋白尿进展的相对风险显著降低[11]。CANVAS试验结果显示：与安慰剂相比，卡格列净组蛋白尿减少27%[13]。在CREDENCE试验中观察到，卡格列净组的平均尿蛋白与肌酐比值(urinary albumin-to-creatinine ratio，UACR)降低了31%，较安慰剂组明显降低[14]。DELIGHT试验中，在治疗24周后，达格列净组的平均UACR变化为21%，较安慰剂组显著降低[15]。SGLT-2抑制剂对尿蛋白的改善可能是由于恢复球管反馈，改善了肾小球高压，且这一效应独立于其对血糖、血压或体重的影响[35]。

2.6 降低血尿酸

一项关于2型糖尿病db/db小鼠模型的研究[36]表明，降低尿酸可以减轻小鼠的肾小管损伤。另外，在一项对肾功能正常、无明显蛋白尿的2型糖尿病患者进行5年随访观察的实验中发现，高尿酸血症组CKD的累积发生率明显高于无高尿酸血症组，在单因素logistic回归分析中，高尿酸血症的存在使CKD发生的风险增加了一倍[37]。因此，降低血尿酸可以减缓CKD的发生和发展。一项卡格列净的随机临床实验证实，在26周时，相较于基线血尿酸水平5.3~5.4 mg/dL，卡格列净100和300 mg组的血尿酸水平降低了13%以上，其中，在高尿酸血症组中，在第26周，卡格列净100 mg组有23.5%的患者达到血尿酸水平<6 mg/dL，卡格列净300 mg组为32.4%，而安慰剂组仅为3.1%[16]。其原因可能是SGLT-2抑制剂使尿液中葡萄糖水平增加，从而激活肾脏SLC2A9转运蛋白，抑制尿酸重吸收，促进尿酸从尿液中排出[38]。

3 结语

综上所述，SGLT-2抑制剂可以有效改善肾脏血流动力学、改善氧化应激、抑制炎症和纤维化反应、降低血尿酸、减少尿蛋白、减轻体重、改善血压，延缓糖尿病肾病的发生及发展，但仍缺乏其肾保护的直接临床证据，仍需进一步的临床研究探索其肾脏保护作用及其机制。此外，有限的研究[39-40]表明，SGLT-2抑制剂可以安全地在高剂量下使用而不会引起低血糖，而基于其球管反馈的恢复和收缩肾小球入球小动脉来保护肾功能的重要机制，将SGLT-2抑制剂的应用扩展到非糖尿病性CKD是可行的，所以扩展其在非糖尿病性CKD中的应用也值得进一步研究探索。

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