·综 述·

SGLT2i 在合并糖尿病动脉粥样硬化性心血管疾病中的作用研究进展

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【摘 要】 糖尿病是一种全球流行病,血糖控制不佳是导致心血管疾病患者死亡的主要原因之一。作为新型降糖药,钠-葡萄糖共转运体2抑制剂(SGLT2i)由于其在临床和基础研究中表现出卓越的心血管系统保护作用而倍受关注。前期针对SGLT2i的大型随机对照试验(EMPA-RED研究、CANVAS研究、DELCARE TIMI-58研究)均证实了SGLT2i作为一级预防和二级预防能够显著降低冠状动脉疾病合并糖尿病患者的心血管死亡、非致命性心肌梗死和非致命性中风的风险。然而,SGLT2i对动脉粥样硬化性心血管疾病的直接作用报道较少。本文对SGLT2i在合并糖尿病的动脉粥样硬化性心血管疾病的作用研究进展进行总结,以期为临床治疗提供更多参考。

【关键词】 心血管疾病;SGLT2抑制剂;糖尿病;动脉粥样硬化

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Research progress in role of SGLT2i in atherosclerotic cardiovascular disease with diabetes mellitus

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【Abstract】 Diabetes is a global epidemic, and poor blood glucose control has been one of the primary causes of death for patients with cardiovascular diseases. Sodium-glucose cotransporter-2 inhibitors (SGLT2i), a novel hypoglycemic agent, has attracted extensive attention due to their prominent protective action on cardiovascular system in addition to the hypoglycemic effect demonstrated in experimental and clinical studies. Previous large randomized controlled trials for SGLT2i (EMPA-RED, CANVAS, DELCARE TIMI-58) confirmed that SGLT2i, either as primary prevention or as secondary prevention, could significantly reduce the risk of cardiovascular deaths, non-fatal myocardial infarction and non-fatal stroke in patients with coronary artery disease and diabetes mellitus. However, there have been limited findings on the actions of SGLT2i, particularly their direct effects, in atherosclerotic cardiovascular disease (ASCVD). This review summarizes the research progress in the role of SGLT2i in ASCVD with diabetes, in an effort to provide more evidence for the clinical treatment of these patients.

【Key words】 cardiovascular diseases; SGLT2 inhibitor; diabetes mellitus; atherosclerosis

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2型糖尿病(type 2 diabetes mellitus,T2DM)与心血管疾病(cardiovascular diseases,CVD)发病率和死亡率增加相关[1]。T2DM及其前期表现——糖耐量减低(impaired glucose tolerance,IGT),使CVD的风险增加了2~4倍,血糖异常使动脉粥样硬化性心血管疾病(atherosclerotic cardiovascular disease, ASCVD)

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发病率和死亡率明显增高[2,3]。一项对冠状动脉疾病(coronary artery disease,CAD)血糖异常患者危险因素的报告(ESC EORP EUROASPIREV)发现,CAD患者患IGT或糖尿病的比例高达2/3,且仅有一半患者知情;该研究通过对其中血糖状况未知的患者进行OGTT筛查后发现,血糖异常患者占41.1%(T2DM 30%,IGT 70%),仅有58%的糖尿病患者服用了心脏保护药[4]。可见目前针对CAD和血糖异常合并症患者的管理和治疗仍很欠缺。为此,糖尿病的管理策略应结合防治CAD。

随着新型降糖药的出现,这种策略将更容易实现。大规模降糖药心血管实验结果显示,可显著降低主要不良心血管事件(major adverse cardiac event,MACE)、心肌梗死、中风和心血管死亡的综合风险的药物只有两种,即胰高血糖素样肽-1受体激动剂(glucagon like peptide-1 receptor agonist,GLP1-RA)[5,6]和钠-葡萄糖共转运蛋白2抑制剂(sodium-glucose cotransporter-2 inhibitors,SGLT2i)。SGLT2i降糖机制为靶向阻断肾脏钠-葡萄糖共转运蛋白来增强尿葡萄糖排泄[7]。目前,临床上获FDA批准的SGLT2i包括卡格列净(canagliflozin)、达格列净(dapagliflozin)、埃格列净(ertugliflozin)和恩格列净(empagliflozin)[8]。

DELCARE TIMI-58试验发现:达格列净治疗合并心肌梗死(myocardial infarction,MI)的糖尿病患者心血管死亡的绝对风险降低幅度高于无MI的患者,强烈推荐T2DM合并MI的患者使用SGLT2i治疗[9]。EMPA-REG试验中,恩格列净将MACE(心血管死亡、非致命性心肌梗死、非致命性中风)降低了14%[10]。SGLT2i对ASCVD作用是否独立于其降糖和肾脏保护作用仍然在研究探讨中,本文将对近期的研究进行总结,并着重阐述SGLT2i在ASCVD的直接作用机制。

1 糖尿病导致心血管系统损伤

糖尿病对心血管系统的损伤主要通过引起内皮细胞功能障碍、内源性一氧化氮生成减少或过量、血管氧化应激、内质网应激等方面发挥作用[11]。糖尿病患者内皮素-1、血栓素A2/前列环素比例升高引起血管功能障碍[12],循环内皮祖细胞减少及功能障碍,影响内皮自我修复功能[13]。内皮源性超氧化物生成增多,引起内质网应激,加速内皮功能障碍和动脉粥样硬化[14]。糖蛋白Ⅰa、Ⅱb、Ⅲa增加,增加了血小板活化、聚集倾向、血栓形成、斑块破裂的风险[15]。糖尿病所致内皮功能障碍、全身炎症导致心肌微血管稀疏,冠状动脉血流储备减少[16]。

2 SGLT2i对糖尿病心血管系统的保护作用

2.1 SGLT2i改善动脉僵硬度

动脉僵硬度是糖尿病患者心血管事件的预测因子,和微循环病变有关[17,18]。研究发现恩格列净可以降低年轻患者的1型糖尿病(type 1 diabetes mellitus,T1DM)动脉僵硬度,这种作用独立于血压和血糖的控制[19],并且发现恩格列净对动脉僵硬度的改善与迷走神经张力和交感神经系统活性无关,研究结果证实其心血管获益并非由于降血糖的单一作用所致。SGLT2i对动脉僵硬度的改善可能通过降低氧化应激抑制炎症和纤维化所致,其结果证明了SGLT2i对心血管系统存在直接作用的可能;试验存在的局限性:只纳入了年轻的T1DM患者,其结果无法推及老年T1DM患者和T2DM患者;并且动脉僵硬度的测量值具有很大可变性[20]。

2.2 SGLT2i调节糖尿病心肌的离子稳态

心肌内的Ca^{2+}和Na^{+}平衡对心脏的信号传导、心律调节以及心肌细胞能量的产生及呼吸链至关重要[21],心肌细胞内Ca^{2+}浓度受L型钙离子通道、ryanodine受体、Na^{+}/Ca^{2+}交换和肌浆网ATPase 2a调节,Na^{+}浓度主要受Na^{+}/K^{+}泵、NCX、Na^{+}/H^{+}交换调节[22]。Baartcheer等[23]发现恩格列净通过调节NHE活性降低了高葡萄糖水平的心肌细胞胞质内的Na^{+}、Ca^{2+}水平,增加心肌线粒体内的Ca^{2+}浓度。前期实验证明在心肌缺血再灌注过程中减少胞质内的Na^{+}、Ca^{2+}蓄积可以减轻梗死面积扩展[24]。Durak等[25]发现达格列净通过增加肥胖胰岛素抵抗MetS大鼠心肌细胞电压门控K^{+}通道电流,改善延长的QT间期,降低MetS大鼠左室舒张压;降低心肌胞浆的Na^{+}、Ca^{2+}浓度,增加线粒体内Ca^{2+}浓度,改善线粒体功能恢复[26]。实验还观察到SGLT2i减轻肥胖胰岛素抵抗小鼠心肌细胞线粒体裂变,促进线粒体融合[27]。有研究证明SGLT2i通过激活电压门控钾离子通道和蛋白激酶G诱导血管扩张改善内皮功能和主动脉僵硬度[13,28,29]。存在的一些局限性:实验的动物数量较少,治疗周期较短,仅使用了一种SGLT2i,仅限于动物实验。

2.3 SGLT2i改善糖尿病心肌的代谢

生理条件下,95%的心肌供能通过线粒体氧化代谢提供,游离脂肪酸(free fatty acid,FFA)、葡萄糖是主要参与氧化代谢的底物[30]。糖尿病心肌因胰岛素抵抗导致脂解作用增加,细胞供能过度依赖脂肪酸和甘油三酯(triglyerides,TG),增加了心肌脂肪

变性和细胞毒性的风险[31]，并增加活性氧物质的产生，诱导急性细胞损伤和炎症反应[32]。Benetti 等[33]发现恩格列净通过减少 TG 的蓄积减轻了高脂高糖小鼠心肌脂肪变性。Santos-Gallego 等[34]发现恩格列净增加实验动物（猪）的梗死心肌对酮体的消耗，降低了心脏对葡萄糖的消耗和乳酸的堆积；该作者还发现恩格列净可以使非糖尿病动物（猪）心肌能量利用从葡萄糖转向酮体、FFA 和支链氨基酸[35]。

2.4 SGLT2i 抗纤维化和心脏重塑作用

心肌梗死后心脏重塑是一个复杂的炎症过程，巨噬细胞在心肌梗死后的炎症发挥重要作用，M1 巨噬细胞具有促炎作用，M2 巨噬细胞参与炎症的消除。信号传导及转录激活蛋白 3（signal transducer and activator of transciption，STAT3）信号通路是调节巨噬细胞表型的关键[36]。研究证明 M2 巨噬细胞对 MI 后心脏重塑至关重要[37]。Lee 等[38]发现达格列净可以显著增加 MI 大鼠 STAT3 活性、STAT3 核易位、心肌 IL-10 水平和 M2 巨噬细胞百分比，抑制 MI 后超氧化物和硝基酪氨酸水平；MI 后第 28 天，SGLT2i 处理组明显减轻了心脏成肌纤维细胞侵润和心脏纤维化；该研究选用了正常血糖大鼠作为实验对象，证明了 SGLT2i 的抗氧化作用直接来自于药物本身。有研究证明达格列净可减少 NOD 样受体 3 炎症小体的激活，减轻 T2DM 小鼠心脏的纤维化和重塑[39]。SGLT2i 通过激活单磷酸腺苷活化蛋白激酶（AMP-activated protein kinase，AMPK）抑制炎症小体上调，发挥心脏抗纤维化和重塑作用，该作用与达格列净的降糖作用无关。

2.5 SGLT2i 对心脏微循环的作用

心脏微血管主要由循环末端的心脏微血管内皮细胞（cardiac microvascular endothelial cells，CMEC）组成，影响心肌灌注和冠状动脉血流储备[40]。高血糖对 CMEC 的损坏胜过对心肌细胞的损坏[41]。Zhou 等[42]发现恩格列净能够改善糖尿病小鼠心脏的微循环、屏障功能、微血管密度、eNOS 磷酸化、内皮依赖性舒张和 CMEC 存活率。研究表明恩格列净可能通过 AMPK/Drpl 信号通路抑制糖尿病引起的线粒体裂变和线粒体氧化应激延缓 CMEC 衰老，从而发挥改善心脏微循环的作用。Ott 等[43]发现达格列净能减轻 T2DM 患者视网膜毛细血管过度灌注，减轻小动脉重构。

2.6 SGLT2i 抑制高心血管风险糖尿病氧化应激和炎症反应

氧化应激在糖尿病诱导 CVD 的发病机制中起关键作用[44]，氧化应激还促进心脏炎症和纤维化[12]。动脉粥样硬化是全身炎症的表现，内皮激活/功能障碍是动脉粥样硬化的开始，并导致斑块易损和破裂[45]。在动脉粥样硬化发展早期，血管内皮及平滑肌的黏附因子和炎症因子表达增加，如 VCAM-1、ICAM-1、MCP-1 和 IL-6。在斑块破裂/糜烂后期，金属蛋白酶 MMP-2、MMP-9 以及他们的抑制剂 TIMP-1 和 TIMP-2 起关键作用[46]。此外单核细胞趋化蛋白-1（monocyte chemoprotein-1，MCP-1）被认为是斑块不稳定性的直接介质[47]。有研究表明 SGLT2i 可以降低啮齿类糖尿病模型血管中促炎性 IL-6、MCP-1 和 ICAM-1 的表达。Mancini 等[48]发现卡格列净可以通过激活 AMPK 抑制高心血管风险的 T2DM 患者内皮细胞中 IL-6 和 MCP-1 的分泌。Nasiri-Ansari 等[49]发现卡格列净给药 5 周后减缓了高脂饮食喂养的载脂蛋白 E 基因敲除小鼠 Apo-E$^{(-/-)}$动脉粥样硬化的进程，卡格列净治疗组小鼠体内 MCP-1 和 VCAM-1 的 mRNA 表达较低。研究表明 SGLT2i 对参与动脉粥样硬化形成的内皮细胞和单核细胞/巨噬细胞具有直接作用，其对 CVD 的保护作用可能独立于降糖和降脂作用[48,50]。

3 结论和未来展望

迄今为止，尚无其他降糖药物显示出与 SGLT2i 同样的糖尿病患者的心血管获益，SGLT2i 不仅通过降糖、降压、降体质量和肾脏保护发挥心血管保护作用，而且直接作用于心血管系统，发挥抗炎、抗氧化、抗动脉粥样硬化、改善心肌及内皮细胞结构和功能等作用。2019 年欧洲心脏病学学会/欧洲糖尿病研究学会指南中推荐，对于 T2DM 伴 ASCVD 患者或高危、极高危心血管风险的患者，可应用 SGLT2i 以减少 MACE 事件和降低死亡风险。随着基础研究和循证证据的不断完善，SGLT2i 在 ASCVD 中的作用机制将进一步明朗，为合并糖尿病的 ASCVD 的临床治疗带来更大的希望。

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