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钠－葡萄糖共转运蛋白2抑制剂治疗2型糖尿病合并非酒精性脂肪肝的研究进展

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[摘 要] 随着全球范围内肥胖和2型糖尿病(type 2 diabetes mellitus，T2DM)发病率的急剧增长，约70%的肥胖糖尿病患者同时合并有非酒精性脂肪肝(non-alcoholic fatty liver disease，NAFLD)，甚至多达30%~40%的患者合并有非酒精性脂肪性肝炎(non-alcoholic steatohepatitis，NASH)。目前T2DM合并NAFLD已成为全球关注的健康问题之一。尽管如此，近年来大量相关研究表明钠-葡萄糖共转运蛋白2(sodium-glucose co-transporter 2，SGLT2)抑制剂显著降糖的同时，肝相关不良事件的发生明显减少，为NAFLD的治疗提供了新思路。

[关键词] 钠-葡萄糖共转运蛋白2抑制剂；肥胖；2型糖尿病；非酒精性脂肪肝

Research progress of sodium-glucose co-transporter 2 inhibitors in the treatment of type 2 diabetes mellitus with non-alcoholic fatty liver

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Abstract With the incidence of obesity and type 2 diabetes mellitus (T2DM) increasing dramatically worldwide, about 70% of obese diabetics combined with non-alcoholic fatty liver disease (NAFLD) and even as many as 30%–40% combined with non-alcoholic steatohepatitis (NASH). At present, T2DM with NAFLD has become one of the global health concerns. Even so, in recent years, a great deal of researches on sodium-glucose co-transporter 2 (SGLT2) inhibitors have shown that they have remarkable effect of lowering blood sugar, also, the incidence of adverse events related to liver has significantly reduced, thus providing new ideas for the treatment of NAFLD.

Keywords sodium-glucose co-transporter 2 inhibitor; obesity; type 2 diabetes mellitus; nonalcoholic fatty liver disease

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非酒精性脂肪肝(non-alcoholic fatty liver disease，NAFLD)是指除外酒精和其他明确的肝损因素所导致的，以弥漫性肝细胞大泡样脂肪变为主要特征的临床病理综合征，包括单纯性脂肪性肝病(non-alcoholic simple fatty liver)以及由其演变的非酒精性脂肪性肝炎(nonalcoholic steatohepatitis，NASH)、脂肪性肝纤维化和肝硬化[1]。

钠-葡萄糖共转运蛋白2(sodium-glucose co-transporter 2，SGLT2)是一种具有低亲和力、高容量特性的跨膜转运蛋白质，分布在肾近端小管细胞腔面膜，滤过的葡萄糖约90%是通过SGLT2重吸收的，SGLT2抑制剂则通过增加尿糖排泄从而降低血糖[2]。目前SGLT2抑制剂主要包括达格列净、坎格列净、依帕列净、雷莫列净、鲁格列净等。SGLT2抑制剂在降糖的同时可改善肝功能，由于这是一种全新的药物，其是否能有效的治疗2型糖尿病(type 2 diabetes mellitus，T2DM)合并NAFLD吸引了许多科研工作者的关注，本文中就此内容进行综述。

1 SGLT2 抑制剂的临床疗效分析

1.1 改善血糖

SGLT2抑制剂可有效降低HbA1c、控制血糖[3]，从而减轻高糖毒性，改善胰岛素敏感性及β细胞功能[4-5]。Kashiwagi等[6]发现SGLT2抑制剂可显著降低糖化血红蛋白水平，且进一步的随访研究[7]显示：相比于磺酰脲类组，SGLT2抑制剂组其血糖长期良好控制率更优。同样，Han等[8]通过动物实验研究亦证实抑制SGLT2能够增加糖尿病动物的尿糖排泄，改善血糖控制。由此，不管是人体还是动物研究均表明：SGLT2抑制剂可有效改善血糖控制情况。

1.2 改善 NAFLD

众所周知，NAFLD是导致肝转氨酶升高最常见的病因，尤其是ALT升高，可作为诊断NAFLD的常用标志物[9]。近期，一项将为期26周的坎格列净与安慰剂对照研究[10](n=2 313)及为期52周的坎格列净与西格列汀对照研究(n=1 488)的数据整合显示：患者服用300 mg坎格列净与服用安慰剂及西格列汀对比，其血浆ALT是显著下降的。与上述研究一致，Nakano等[11]发现与高脂饮食喂养组小鼠对比，予以口服雷莫列净的高脂饮食组其血浆ALT和AST水平显著下降。多项研究[12-14]表明构建NASH动物模型后，予口服SGLT2抑制剂可通过调节肝脏脂肪变性、炎症及纤维化来减轻肝功能紊乱。

2 SGLT2 抑制剂的降糖机制

肾对葡萄糖的重吸收主要通过SGLTs进行调节[15]。SGLT2分布在肾近端小管细胞腔面膜，协同钠离子逆浓度梯度主动转运小管液中的葡萄糖，小管液中葡萄糖进入细胞后，被上皮细胞基底膜侧的葡萄糖转运蛋白(GLUT)以易化扩散方式转运至细胞外，再经吸收进入毛细血管网，完成葡萄糖的重吸收过程[16]。在正常的生理情况下，肾小球每天滤过160~180 g葡萄糖，且几乎全被重吸收[17]，当血糖浓度超过肾糖阈值后，便出现糖尿[18]。有趣的是，家族性肾性糖尿患者尿糖排泄每日可达100 g，但大部分病人并无其他症状，血糖不高，肾功能也无异常，经研究[19]发现此类患者是因为SLCA2基因突变，SGLT2功能亦受损，肾小管重吸收葡萄糖异常所致。Rahmoune等[20]通过研究从糖尿病人尿液中分离的肾脏细胞，发现糖尿病患者SGLT2的表达较正常人增多，从而导致肾重吸收葡糖糖能力增加，血糖进一步升高[21]。

3 SGLT2 抑制剂治疗 T2DM 合并 NAFLD 可能的机制

近年来有研究[22]发现：SGLT2抑制剂可能通过降糖及降糖之外的机制对糖尿病合并NAFLD起到良好的治疗效果。

3.1 改善胰岛素抵抗

关于NAFLD的发病机制，Day[23]提出的“二次打击”学说中胰岛素抵抗、慢性氧化应激和脂质过氧化仍是目前普遍接受的关键因素。近来也有学者[24]提出“多次打击”的学说，即在二次打击的基础上，机体对受损的肝细胞进行修复，进一步促进肝纤维化，最终导致肝硬化。但无论是二次打击还是多次打击，都认为胰岛素抵抗是NAFLD发生、进展的中心环节。多项研究[25-27]均表明：SGLT2抑制剂可明显改善胰岛素抵抗。Nakano等[28]关于雷莫列净的研究显示：雷莫列净的化学结构表明它可能具有内在的抗氧化性能，可提高胰岛素敏感性，此外，还观察到使用雷莫列净处理的动物其硫代巴比妥酸反应物(thiobarbituric acid reactive substances，TBARS)是减少的。因此，至于雷莫列净是否仅作为一种抗氧化剂，还是与其减少TBARS产生共同作用来提高胰岛素敏感性，目前尚不清楚。当然，SGLT2抑制剂改善胰岛素抵抗的机制远不止这些，普遍认为还与其降糖、降脂、抗炎作用等密切相

关，具体机制有待进一步研究探讨。

3.2 抗炎

NAFLD发病基础为肝细胞脂质异常沉积。而Tateya等[29]研究表明脂肪的过度积聚可导致氧化应激的发生，氧化应激再通过调控IL-6和MCP-1等因子促进脂肪组织的低丰度炎症状态，随后巨噬细胞M1，淋巴细胞Th1均被激活，进一步导致促炎因子TNF-α及IFN-γ的释放。动物实验研究[30]证实：与非肥胖小鼠相比，未予特殊处理的肥胖小鼠其TNF-α和MCP-1 mRNA水平大约高出5倍，并与Tateya等研究一致，均表明脂质积聚可促发炎症反应。为探讨SGLT2抑制剂是否具有抗炎作用，Qiang等[22]建立NASH模型组(NA/STZ/HFDT)及鲁格列净+NASH模型组(NA/STZ/HFDT/Luseo)，发现NA/STZ/HFDT组小鼠中MCP-1，IL-1β，IL-6，IL-12以及F4/80等细胞因子的表达呈显著上升，而NA/STZ/HFDT/Luseo组小鼠中上述细胞因子的表达正常，结果表明鲁格列净对小鼠肝的炎症起抑制作用。另有研究[13]表明：由肥胖诱导的普通巨噬细胞标志物F4/80基因表达升高而引起的肝的炎症，可被依帕列净抑制，实验过程中还发现：依帕列净处理高脂喂养的小鼠后，其促炎巨噬细胞M1标志Cd11c表达下调，且促炎因子TNF-α的表达同样呈下降趋势，而不影响抗炎巨噬细胞M2标志Cd206的表达。结合上述，SGLT2抑制剂可能通过抗炎作用来改善NAFLD功能。

3.3 降低肝脂质合成，促进分解

肝脂质积聚在NAFLD的发生和发展中起关键作用，而NAFLD发生的分子基础主要是核受体以及核受体依赖的脂质代谢相关基因的异常激活或抑制而导致肝脂质代谢紊乱所致[31]，因而改善脂质代谢成为治疗NAFLD的根本措施。Honda等[32]在小鼠模型上探讨肝脂质合成与分解是否受SGLT2抑制剂的调节，发现使用SGLT2抑制剂处理的小鼠，其参与脂质合成的基因ACC1和SREBP-1c mRNA的表达水平比基础饮食喂养组小鼠要低，而脂肪酸氧化分解的基因PPARα，CPT-1α以及MTTP mRNA的表达水平均显著高于NAFLD模型小鼠。可见，SGLT2抑制剂可能通过降低肝脂质合成，增加分解，因而改善NAFLD。

3.4 减轻肝纤维化

Honda等[32]在一项关于SGLT2在小鼠中治疗NASH的疗效研究中表明：相比NAFLD模型小鼠，由SGLT2抑制剂处理的小鼠，在光学显微镜下观察SR染色结果，发现其染色面积要小得多，同时，其胶原蛋白1α1以及α-SMA mRNA的表达水平亦显著降低。而SR染色面积及检测胶原蛋白1α1和α-SMA mRNA表达水平均可用于明确肝纤维化的严重程度。由此表明：SGLT2抑制剂可明显减轻肝纤维化程度，并通过此作用达到延缓及改善NAFLD的目的。

4 结语

SGLT2抑制剂为T2DM的治疗提供了一种新的作用途径，即通过抑制SGLT2活性或基因表达来增加尿糖排泄，从而降低血糖。SGLT2抑制剂不仅可以降低血糖，减轻高糖毒性，还能改善胰岛素敏感性及抗炎、降低肝脂质合成并促进分解、减轻肝纤维化，有直接或间接肝保护作用，能减轻糖尿病患者的肝功能损害，延缓及改善NAFLD。但长期使用SGLT2抑制剂的有效性及风险还需要大量的基础研究和临床数据观察。就目前而言，SGLT2抑制剂具有良好的发展前景，有不少药物已进入临床试验，新型药物的上市让我们对T2DM以及T2DM合并NAFLD的治疗充满期待。

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