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GLP-1RA及SGLT-2i对糖尿病患者的血尿酸的影响如何？

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摘　要

GLP-1RA及SGLT-2i是ADA和中华医学会糖尿病学分会推荐的新型降糖药物，具有低血糖风险小、兼具心血管保护及降低体重等代谢获益的特点。高尿酸血症是2型糖尿病的独立危险因素，在临床实践中，人们一直在关注预防SUA的升高。据估计，患者SUA每升高1 mg/dl，发生T2DM的风险就会增加17%。国内外学者研究结果提示SGLT-2i能兼顾降糖的同时降低SUA水平；最近国外研究显示GLP-1RA还可以降低SUA水平，但仍存在矛盾。国内学者对此研究报告甚少。还需要更多的研究填补此领域的空白，为更好地预防2型糖尿的发生及发展作出贡献。

关键词

GLP-1RA，SGLT-2i，糖尿病，血尿酸

How Did the GLP-1RA and SGLT-2i Affect Serum Uric Acid in Diabetic Patients?

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Abstract

GLP-1RA and SGLT-2i are new hypoglycemic drugs recommended by ADA and Diabetes Branch of Chinese Medical Association, which have the characteristics of low risk of hypoglycemia, metabolic benefits such as cardiovascular protection and weight reduction. Hyperuricemia is an independent risk factor for type 2 diabetes, and much attention has been paid to the prevention of elevated SUA in clinical practice. It is estimated that every 1 mg/dl elevation of patient SUA causes a 17% increase in the risk of developing T2DM. The results of domestic and foreign scholars suggest that SGLT-2i can reduce SUA level while lowering glucose; recent foreign studies show that GLP-1RA can also reduce SUA level, but there are still contradictions. Domestic scholars have few reports on this. More studies are needed to fill the gap in this field to contribute to better prevention of the occurrence and development of type 2 diabetes mellitus.

Keywords

GLP-1RA, SGLT-2i, Diabetes Mellitus, Serum Uric Acid

1. 引言

糖尿病(DM)是全球的一个主要公共卫生问题。世界卫生组织报告说，有 4.22 亿人患有糖尿病，主要是在低收入和中等收入国家，每年导致 160 万人死亡。2 型糖尿病(Type 2 diabetes, T2D)是一种以慢性高血糖为特征的内分泌系统疾病，是世界上发病率高、死亡率高、致残率高的疾病之一。近 30 多年来，我国糖尿病患病率显著增加。1980 年全国 14 省市 30 万人的流行病学资料显示，糖尿病的患病率为 0.67%。2015 至 2017 年中华医学会内分泌学分会在全国 31 个省进行的甲状腺、碘营养状态和糖尿病的流行病学调查显示，我国 18 岁及以上人群糖尿病患病率为 11.2%。以 2 型糖尿病(T2DM)为主，1 型糖尿病(T1DM)和其他类型糖尿病少见，男性高于女性(2015 至 2017 年全国调查结果为 12.1%和 10.3%)。在 2015 至 2017 年全国 46 家三级医院招募的 30 岁及以上的 17,349 例新诊断糖尿病患者中，T1DM (经典 T1DM 和成人隐匿型自身免疫性糖尿病)占 5.8%，非 T1DM (T2DM 和其他特殊类型糖尿病)占 94.2%。糖尿病人群中 T2DM 占 90%以上。据估计，与非糖尿病患者相比，糖尿病患者的医疗保健支出增加了一倍。糖尿病对一些国家、医疗保健系统和个人产生了重大的经济影响(国际糖尿病联合会，2020 年)。

2. 降糖药物

2.1. 胰高血糖素样肽-1 受体激动剂(GLP-1RA)

胰高血糖素样肽-1 受体激动剂(glucagon-like peptide-1 receptor agonist, GLP-1RA)是 T2DM 治疗领域的一类新型降糖药，可显著改善 T2DM 的一些关键性病理生理缺陷[1]，并具有减少心血管死亡、改善动脉粥样硬化、减轻体质量、降低收缩压、改善血脂谱等降糖外获益[2]。GLP−1RA 通过激活 GLP−1 受体以葡萄糖浓度依赖的方式刺激胰岛素分泌和抑制胰高糖素分泌，同时增加肌肉和脂肪组织葡萄糖摄取，抑制肝脏葡萄糖的生成而发挥降糖作用，并可抑制胃排空，抑制食欲[3] [4]。GLP-1RA 除了减肥、降低

血糖水平的好处外已被证明对多个器官有直接的保护作用，还包括大脑、胰腺 b 细胞功能、肝脏和心脏。大脑皮层中的胰高血糖素样肽-1 受体似乎通过抗凋亡作用、神经元更新、抗氧化作用、抗炎作用以及限制 b 淀粉样蛋白和新原纤维缠结积累对脑缺血、帕金森病甚至精神病具有保护作用[5]-[7]。GLP-1RA 的使用也可以改善非酒精性脂肪性肝炎患者的肝功能和组织学特征[8]。此外，GLP-1RA 治疗可降低心脏 b1-肾上腺受体的表达，将心肌表盘能量来源从脂肪酸变为葡萄糖，从而改善心功能[9] [10]。

2.2. 钠－葡萄糖协同转运蛋白 2 抑制剂(SGLT-2i)

SGLT-2 抑制剂是一类近年受到高度重视的新型口服降糖药物[11]-[15]，可抑制肾脏对葡萄糖的重吸收，降低肾糖阈，从而促进尿糖的排出[16]。对血糖控制有中等作用，低血糖和体重增加的风险低[17] [18]。SGLT2 抑制剂通过不依赖胰岛素的机制降低血糖，降低血清胰岛素，改善胰岛素抵抗[19]-[21]。目前的证据表明，SGLT-2 抑制剂可改善了心血管终点，包括全因死亡率、心血管死亡率、心力衰竭(HF)和动脉粥样硬化大血管事件[22]。此外，SGLT-2 抑制剂在肾脏并发症的进展方面显示出惊人的影响，如降低血清肌酐、减少蛋白尿和减少肾脏疾病引起的死亡[23] [24]。钠－葡萄糖共转运体 2(SGLT2)是一种高容量、低亲和力的葡萄糖转运体，存在于肾脏近端凸流小管，是葡萄糖重吸收的大部分原因。除了降低血糖水平，SGLT2 抑制剂也被报道可以降低血清尿酸水平[25]。包括一部分高尿酸血症患者。此外，20%~30%的高尿酸血症患者使用 SGLT-2i 能够达到正常的血清尿酸水平(<6 mg/dl)。SGLT2 抑制剂降低血清尿酸的机制尚不清楚，然而，推测它可能与肾脏 SLC2A9 (GLUT9)转运体有关。SLC2A9 基因编码一种促进葡萄糖转运体，有两个剪接变体，在肾元近端小管的顶端膜高表达，肾元是肾脏尿酸处理的关键部位，发现同时运输尿酸和 d-葡萄糖。SGLT2 抑制剂治疗导致尿中葡萄糖排泄增加，最终可能导致增加尿酸的变化管细胞的顶端膜导致增加尿酸从血液释放到尿液，从而降低血清尿酸水平[26]-[28]。在表达 SLC2A9b 的非洲爪蟾卵母细胞中，高葡萄糖浓度反式刺激尿酸外排的证据支持了这一潜在机制[29]。

3. 高尿酸血症的危害

尿酸是嘌呤代谢的副产品，由黄嘌呤的氧化作用产生[30] [31]。血清尿酸水平升高可能是由于饮食摄入、细胞物质分解增加或肾脏消除减少的结果，并可导致高尿酸血症[32]。高尿酸血症和糖尿病是相互依赖的，在糖尿病患者中，高尿酸血症比在非糖尿病人群中更为普遍，糖尿病可被认为是高尿酸血症的独立危险因素[33]。特别是，据报道，在糖代谢受损的早期阶段，SUA 水平升高，从而预测 2 型糖尿病(T2DM)的发病[34]-[37]；这也得到了 meta 分析的支持[38] [39]。此外，有证据表明，高尿酸血症与糖尿病的大血管和微血管并发症相关[37] [40]-[45]。在过去的几十年里，越来越多的证据表明，SUA 水平在“糖尿病前期”中已经升高，提示 SUA 在 T2DM 的发病机制中发挥了作用[46] [47]。在此背景下，已提出了高尿酸血症可能影响葡萄糖代谢和 CV 健康的几种机制[48]。更具体地说，高尿酸血症增加氧化应激，降低一氧化氮(NO)的可用性，导致内皮功能障碍和胰岛素抵抗(因为胰岛素需要 NO 来摄取葡萄糖) [49] [50]。研究发现，与任何其他已知的危险因素无关，血清尿酸水平较高的个体未来发生 2 型糖尿病的风险较高[36]。

其他几个对成年人的研究也发现了高尿血症与动脉粥样硬化有关[51]-[53]。通过系统回顾和荟萃分析，研究了血清尿酸作为心血管疾病的独立危险因素的作用，并显示高尿酸血症确实增加了心血管疾病的风险和死亡率[54]。一些研究已经确定高尿酸血症是代谢综合征、糖尿病和高血压发展的预测因子[55]。糖尿病和高尿酸血症的患者发生严重痛风、肾结石和血管并发症的风险增加[56] [57]。此外，研究已经确定了糖尿病患者的血清尿酸水平与死亡风险之间的关联。这项汇总分析显示，血清尿酸每增加 0.1 mmol/L，糖尿病并发症就会增加 28%，而糖尿病导致的死亡风险就会增加 9% [57]。考虑到与高尿酸血症相关的各种疾病，降低血清尿酸可能有利于糖尿病患者，他们可能有更高的微血管和心血管疾病的风险。

4. 国内外进展

国外文献报道，GLP-1RA 已被证明可以在输注后立即降低 SUA 浓度，可能是由 GLP-1ra 诱导的近端小管中钠氢离交换蛋白-3 (NHE-3)抑制剂和/或随后的尿碱化介导的[58] [59]。然而，长期使用 GLP-1RA 治疗后，还有相互矛盾的结果报道，学者提出，在长期治疗期间肾小管水平的快速耐受性和/或代偿机制的诱导使 T2DM 患者的尿酸水平的影响不明显，只有短效作用的 GLP-1RA 具有持续的利钠和尿碱化作用[59]。虽然一些研究报告了降低 SUA 的作用[60]-[62]，其认为是通过抑制肾近端小管的 Na+/H+交换 3 型来增加尿酸的绝对排泄，但其他研究报告了 GLP-1RA 治疗前后对 SUA 浓度没有显著影响[63]-[65]，可能是应用 GLP-1RA 使 eGFR 有微小但不显著的下降，eGFR 的暂时性下降可能是肾血流动力学改变的急性后果，并随着时间的推移逐渐消失。比如 Kurir 等人调查了肥胖男性 2 型糖尿病患者应用 GLP-1RA 的结果，发现 GLP-1RA 给药前后的 SUA 水平无显著差异[63]；Liakos 等人和中山等人报道了类似的结果[66] [67]。Sara Najafi 等人研究数据分析表明 GLP-1RA 可显著降低糖尿病患者和肥胖个体的 SUA 浓度。然而，与安慰剂相比，这些减少并不显著[68]。

值得注意的是，越来越多国内外学者研究证据显示，SGLT-2 抑制剂可以降低 T2DM 患者中升高的 SUA 水平，并被认为是 T2DM 患者中极有前途的一种治疗选择[69]-[71]。其机制认为有一下三方面：1) SGLT-2i 可能通过阻断肾小管尿酸转运体，如尿酸转运蛋白 1 (URAT1)来改善尿葡萄糖排泄，URAT1 在葡萄糖重吸收时增加 UA 的分泌，导致 UA 排泄增加和 SUA 减少。此外，SGLT-2i 通过降低血清胰岛素水平来抑制 URAT1 对 UA 的重吸收。2) SGLT-2i 抑制细胞内葡萄糖进入近端肾小管细胞，恢复 DNA-依赖性去乙酰化酶(SIRT1)的产生，而 DNA-依赖性去乙酰化酶抑制尿酸代谢中的主要酶黄嘌呤氧化酶(OX)，导致 UA 水平降低。DNA-依赖性去乙酰化酶也可能刺激 UA 的肠道排泄。3) SGLT-2i 可以极大地抑制炎症小体的激活、IL-1 和 NOD 样受体热蛋白结构域相关蛋白 3 (NLRP3)的产生以及 NLRP3 的激活，从而减轻高尿酸血症。SGLT2i 可以通过 RAAS，下调黄嘌呤氧化酶的活性，抑制炎症反应，减少 SUA 的形成。2 型糖尿病患者可以受益于 SGLT-2 抑制剂引起的高尿酸血症发生率。大量的临床试验和基础研究已经建立了 2 型糖尿病和高尿酸血症之间的关系。考虑到与高尿酸血症相关的全身性疾病，降低 2 型糖尿病患者的血清尿酸无疑是有益的[72]。

5. 结论

GLP-1RA 及 SGLT-2i 是 ADA 和中华医学会糖尿病学分会推荐的新型降糖药物，具有低血糖风险小、兼具心血管保护及降低体重等代谢获益的特点。高尿酸血症是 2 型糖尿病的独立危险因素，在临床实践中，人们一直在关注预防 SUA 的升高。据估计，患者 SUA 每升高 1 mg/dl，发生 T2DM 的风险就会增加 17%。国内外学者研究结果提示 SGLT-2i 能兼顾降糖的同时降低 SUA 水平；最近国外研究显示 GLP-1RA 还可以降低 SUA 水平，但仍存在矛盾。国内学者对此研究报告甚少。还需要更多的研究填补此领域的空白，为更好地预防 2 型糖尿的发生及发展作出贡献。

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