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SGLT2 抑制剂对 2 型糖尿病患者血糖、血尿酸水平及心脏功能的影响 *

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摘要 目的:研究 SGLT2 抑制剂对 2 型糖尿病患者血糖、血尿酸水平及心脏功能的影响。**方法:**选取我院 2019 年 1 月~2020 年 6 月收治的 2 型糖尿病合并稳定性心功能不全患者 106 例为研究对象,采用随机数字表法将患者分为两组,所有患者均给予 2 型糖尿病饮食控制治疗方案,并给予心功能不全对症药物治疗。对照组患者在此基础上给予二甲双胍,观察组在对照组的基础上给予 SGLT2 抑制剂达格列净。比较两组患者的血糖、血尿酸(uric acid, UA)、血清脑钠肽(brain natriuretic peptide, BNP)水平、心脏功能及生活质量。**结果:**治疗前两组的餐后 2 h 血糖(2-hour postprandial glucose, 2 h PBG)、空腹血糖(fasting blood glucose, FBG)及糖化血红蛋白(glycosylated hemoglobin, HbA1c)水平比较无差异($P>0.05$),治疗后两组的上述指标均显著降低,且观察组显著低于对照组($P<0.05$);治疗前两组的 UA 和 BNP 水平比较无差异($P>0.05$),治疗后两组的上述指标均显著降低,且观察组显著低于对照组($P<0.05$);治疗前两组的左室射血分数(left ventricular ejection fraction, LVEF)和左室舒张末期内径(left ventricular end diastolic diameter, LVEDD)水平比较无差异($P>0.05$),治疗后观察组的 LVEF 水平显著升高, LVEDD 水平显著降低($P<0.05$),但对对照组治疗前后比较无差异($P>0.05$);治疗前两组的 SF-36 健康调查量表(the SF-36 Health Survey, SF-36)评分比较无差异($P>0.05$),治疗后两组的 SF-36 评分均显著上升,且观察组显著高于对照组($P<0.05$),两组的不良反应发生率比较无统计学差异($P>0.05$)。**结论:**达格列净可显著改善 2 型糖尿病合并稳定性心功能不全患者的血糖、血尿酸水平,还能够改善患者的心脏功能,值得临床借鉴。

关键词:SGLT2 抑制剂; 2 型糖尿病; 血糖; 血尿酸; 心脏功能

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Effects of SGLT2 Inhibitors on Blood Glucose and Uric Acid Levels and Cardiac Function in Patients with Type 2 Diabetes Mellitus*

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ABSTRACT Objective: To study the effects of SGLT2 inhibitors on blood glucose, blood uric acid levels and heart function in patients with type 2 diabetes. **Methods:** A total of 106 patients with type 2 diabetes combined with stable cardiac insufficiency admitted to our hospital from January 2019 to June 2020 were selected as the research objects. The patients were divided into two groups by random number table method. All patients were given diet control and exercise therapy for type 2 diabetes, and symptomatic drug therapy for cardiac insufficiency. Control group was additively given metformin, and observation group was additively given the SGLT2 inhibitor dagglisin. Blood glucose, blood uric acid, BNP level, heart function and quality of life in 2 groups were compared. **Results:** There were no significant differences in the levels of PBG, FBG and HbA1c in 2 groups before treatment ($P>0.05$). After treatment, the above indexes in 2 groups were significantly decreased, and the observation group was significantly lower than the control group ($P<0.05$). There was no significant difference in UA and BNP levels between 2 groups before treatment ($P>0.05$). After treatment, the above indexes in 2 groups were significantly decreased, and the observation group was significantly lower than the control group ($P<0.05$). Before treatment, there was no statistical difference in LVEF and LVEDD levels between the two groups ($P>0.05$). After treatment, LVEF level in the observation group was significantly increased while LVEDD level was significantly decreased, and there was a statistical difference between the two groups ($P<0.05$). However, there was no statistical difference between the control group before and after treatment ($P>0.05$). There was no statistical difference in the SF-36 score between the two groups before treatment ($P>0.05$), but after treatment, the SF-36 score of the two groups was significantly increased, and the observation group was significantly higher than the control group ($P<0.05$). There was no statistical difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Dagglisin can significantly improve

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the levels of blood glucose and uric acid in patients with type 2 diabetes mellitus complicated with stable cardiac insufficiency, and can also improve the cardiac function of patients, which is worthy of clinical reference.

Key words: SGLT2 inhibitor; Type 2 diabetes; Blood sugar; Blood uric acid; Heart function

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前言

目前,随着生活水平和饮食习惯的改变,糖尿病的发病率呈上升趋势,已经成为我国最为严重的公共卫生问题之一,严重威胁患者的健康和生活质量^[1-3]。糖尿病是一种代谢性疾病,对机体的代谢系统、神经功能、心脏和肾脏等造成损伤^[4,5]。2型糖尿病是糖尿病最常见的类型,与遗传、年龄、环境等共同作用有关,随着患者病情的进展,糖尿病可并发血管病变,尤其是心血管疾病的发生风险较高^[6-8]。2型糖尿病患者由于糖、脂、蛋白代谢紊乱,容易引起心肌功能和结构的损伤,进而引发心肌细胞功能障碍,导致心功能不全的发生^[9,10]。有研究显示^[11],约有25%的糖尿病患者同时患有心功能不全,且糖尿病患者心功能不全的发病率是健康人的2~3倍。对于此类患者的治疗临床需要格外关注患者的降糖效果及心血管方面的获益情况。达格列净是一种的葡萄糖协同转运蛋白(SGLT-2)抑制剂,是一种新型降糖药,具有较好的降糖效果,且对于糖尿病并发心功能不全患者的获益较高^[12-14]。因此,本文选取本院收治的2型糖尿病合并稳定性心功能不全患者,研究了达格列净对2型糖尿病患者血糖、血尿酸水平及心脏功能的影响。

1 资料与方法

1.1 一般资料

选取我院2019年1月~2020年6月收治的2型糖尿病合并稳定性心功能不全患者106例,采用随机数字表法分为两组,对照组53例,男28例,女25例;年龄50~72岁,平均 65.38 ± 5.27 岁;病程:4~9年,平均 6.85 ± 1.35 年。观察组53例,男29例,女24例;年龄68~75岁,平均 66.12 ± 5.54 岁;病程:5~9年,平均 6.94 ± 1.41 年。两组一般资料比较无差异($P > 0.05$)。

1.2 入选标准

纳入标准:①所有患者均符合《中国2型糖尿病防治指南(2017年版)》中的相关诊断标准;②所有患者的心功能分级为I-II级(NYHA分级)。排除标准:①不稳定心功能不全者;②合并严重肝肾功能不全者;③合并其他心血管疾病者;④对本研究所用药物过敏者;⑤1型糖尿病患者;⑥合并糖尿病其他并发症者。

1.3 方法

所有患者均给予2型糖尿病饮食控制治疗方案,并予心功能不全对症药物治疗。对照组患者在饮食控制、对症治疗的基础上给予盐酸二甲双胍片(华北制药有限公司,国药准字H13020734,规格:0.25 g/片),用药方法:初始剂量0.25 g/次,2~3次/d,根据患者的具体治疗情况逐渐增加剂量至1~1.5 g/d,最高不超过2 g/d。对于血糖控制不佳的患者注射胰岛素治疗。观察组在对照组的基础上给予达格列净(阿斯利康制药,国药准字H20170119,规格:10 mg/片),用药方法:晨服,5 mg。两组患者均用药半年。在用药期间监测患者的血糖及不良反应发生情况。

1.4 观察指标

①比较两组患者治疗前后的血糖水平,包括2h PBG、FBG及HbA1c,分别于治疗前后采集两组患者的空腹静脉血6 mL、餐后2 h静脉血2 mL,在3000 r/min下离心10 min,取上清液,采用德国生产的BIOSN血糖分析仪对2h PBG和FBG水平进行检测。采用全自动HbA1c分析仪(HA-8180,厂家:日本Arkray公司)检测HbA1c水平。②比较两组患者治疗前后的血UA、BNP水平,取上述两组患者的空腹静脉血3 mL,2500 r/min下离心5 min,取上清液,采用尿酸酶法测定血尿酸水平,采用酶联免疫吸附试验法检测血清BNP水平。③比较两组患者的心功能相关指标,采用心脏彩色超声仪(DW-PF580型,深圳市大为电子有限公司)测量两组患者治疗前后的LVEF和LVEDD。④比较两组患者的生活质量及不良反应发生率,采用SF-36量表对两组患者治疗前后的生活质量进行评价,该量表包括躯体功能、社会功能、生理机能和精神健康等8个领域,满分为100分,得分越高表示患者的生活质量越好^[15]。

1.5 统计学方法

应用SPSS23.0,计数资料以率(%)表示,行 χ^2 检验,计量资料以($\bar{x} \pm s$)表示,行t检验, $P < 0.05$ 有统计学差异。

2 结果

2.1 两组治疗前后的血糖水平比较

治疗前两组的2 h PBG、FBG及HbA1c水平比较无差异($P > 0.05$),治疗后两组的上述指标均显著降低,且观察组显著低于对照组($P < 0.05$),见表1。

表1 两组治疗前后的血糖水平比较($\bar{x} \pm s$)

Table 1 Comparison of blood glucose levels before and after treatment between the two group($\bar{x} \pm s$)

Groups	n	2hPG (mmol/L)		FBG (mmol/L)		HbA1c (%)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	53	11.42 $\pm$ 2.56	9.19 $\pm$ 2.13*	9.06 $\pm$ 2.68	6.33 $\pm$ 2.11*	8.44 $\pm$ 2.36	7.58 $\pm$ 1.47*
Observation group	53	11.49 $\pm$ 2.78	7.41 $\pm$ 1.05**	8.96 $\pm$ 2.54	5.44 $\pm$ 1.74**	8.38 $\pm$ 2.47	7.05 $\pm$ 1.04**

Note: Compared with pretherapy, * $P < 0.05$; compared with the control group, ** $P < 0.05$.

- 2.2 两组治疗前后的 UA 和 BNP 水平比较 治疗后两组的上述指标均显著降低,且观察组显著低于对照组
治疗前两组患者的 UA 和 BNP 水平比较无差异 ($P>0.05$), ($P<0.05$),见表 2。

表 2 两组治疗前后的 UA 和 BNP 水平比较($\bar{x} \pm s$)

Table 2 The levels of UA and BNP before and after treatment in 2 groups were compared($\bar{x} \pm s$)

Groups	n	UA(umol/L)		BNP(pg/mL)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	53	386.25± 56.14	356.98± 45.69*	998.25± 165.89	712.56± 46.38*
Observationgroup	53	395.67± 55.84	312.33± 40.28**	989.87± 156.14	407.36± 48.74**

- 2.3 两组治疗前后的 LVEF 和 LVEDD 水平比较 著降低($P<0.05$),但对照组治疗前后比较无差异($P>0.05$),见
治疗前两组的 LVEF 和 LVEDD 水平比较无差异 ($P>$ 表 3。
0.05), 治疗后观察组的 LVEF 水平显著升高,LVEDD 水平显

表 3 两组治疗前后的 LVEF 和 LVEDD 水平比较($\bar{x} \pm s$)

Table 3 The levels of LVEF and LVEDD before and after treatment in 2 groups were compared($\bar{x} \pm s$)

Groups	n	LVEF(%)		LVEDD(mm)	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Control group	53	46.02± 8.12	46.85± 8.23	60.85± 23.56	59.85± 20.31*
Observationgroup	53	45.89± 8.06	51.56± 4.58**	59.96± 22.15	50.98± 18.33**

- 2.4 两组治疗前后的生活质量及不良反应发生情况比较 后两组的 SF-36 评分均显著上升,且观察组显著高于对照组
治疗前两组患者的 SF-36 评分比较无差异($P>0.05$),治疗 ($P<0.05$),两组的不良反应发生率比较无差异($P>0.05$),见表4。

表 4 两组治疗前后的生活质量及不良反应发生情况比较

Table 4 The quality of life and the incidence of ADR before and after treatment were compared between the two groups

Groups	n	SF-36(score)		Incidence of adverse reactions(%)
		Pretherapy	Post-treatment	
Control group	53	65.28± 15.34	78.97± 18.35	8(15.09)
Observationgroup	53	67.03± 16.27	87.87± 19.24**	10(18.87)

3 讨论

糖尿病是目前全球的公共卫生问题,我国是高发区,患病者率达到 9.7%~11%^[16-18]。目前随着医学技术水平的不断提升,糖尿病并发症的预防和控制引起了临床的重视,但临床常用的降糖药主要以胰岛素为靶点,随着病情的进展及不良反应的影响,其治疗效果也明显下降^[19,20]。

本研究发现,治疗后两组 2h PBG、FBG 及 HbA1c 水平均显著降低,且观察组显著低于对照组,与吴光秀^[21]的研究类似,该学者探讨达格列净对糖尿病肾病患者血糖水平及肾功能的影响,结果显示治疗 3 个月后,观察组 FPG、2hPG、HbA1c 水平均显著低于治疗前及对照组。说明达格列净治疗糖尿病合并心功能不全可显著降低患者的血糖水平,其作用机制为达格列净可抑制肾小管对葡萄糖的重吸收,提高葡萄糖的排出,从而使患者的血糖水平降低^[22-24]。二甲双胍可影响肝细胞、肌细胞、脂肪、胰腺细胞等对葡萄糖的处理能力,可抑制肝脏内葡萄糖的生成,增加外周组织胰岛素的敏感性,从而降低血糖。两者联合应用通过不同的途径共同作用进而降低患者的血糖水平^[25,26]。

血尿酸是糖尿病患者微血管和大血管发生病变的独立危险因素。BNP 是一种神经内分泌激素,主要由心室分泌,心力衰竭时,心脏容量负荷或压力负荷增加,心室肌受到牵张或室壁压力增大,引起血学 BNP 中浓度增加,是预测患者心功能的重要指标之一。本研究结果显示,治疗后两组 UA 和 BNP 水平均显著降低,且观察组显著低于对照组,治疗后观察组患者的 LVEF 水平显著升高,LVEDD 水平显著降低,但对照组治疗前后比较无统计学差异。与高芳芳^[27]等学者的研究类似,观察血糖控制不佳的 2 型糖尿病患者加用达格列净后的血糖波动情况,结果显示观察组 UA 均较治疗前下降,且观察组显著低于对照组;同时杨震等研究显示^[28],达格列净在 2 型糖尿病合并心功能不全患者中应用可显著改善患者的心功能,改善患者的预后,与本研究的结果一致。说明达格列净治疗糖尿病合并心功能不全可显著改善患者的心功能。主要的作用机制有以下几点:(1) 达格列净可通过抑制肾小管 Na^+ -SGLT-2 对葡萄糖和 Na^+ 重吸收,抑制肾素-血管紧张素-醛固酮系统的过度激活,进而延缓患者动脉粥样硬化的进程,起到降低血压的效果,良好的控制血压可显著改善患者的心肌耗氧量和前后负荷^[29]。

(2)可增加患者的胰岛素敏感性,改善心脏和肌肉对葡萄糖的转运能力,提高患者的运动耐力^[30,31]。(3)较好的利尿作用可改善患者的血容量,直接减轻患者的心脏负荷,改善患者的血液流变学指标。(4)具有直接心脏保护作用,可改善心脏纤维化、抑制心室重构、冠状动脉内膜增的厚度等。(5)减轻患者的体重,增加尿酸的排泄,减少尿酸的重吸收,还能够改善患者的血管内皮功能障碍^[32]。本研究还发现,治疗前两组患者的 SF-36 评分比较无统计学差异,治疗后两组患者的 SF-36 评分均显著上升,且观察组显著高于对照组,与杨震^[33]的研究类似,该学者评价达格列净在 2 型糖尿病合并心功能不全患者中应用的临床效果,结果显示观察组患者 6 个月后在生活质量方面均优于对照组。说明达格列净治疗糖尿病合并心功能不全可显著改善患者的生活质量,这与其可显著降低患者的血糖水平,改善患者的心脏功能有关。另外,两组患者的不良反应发生率比较无统计学差异,史晓获^[34]的研究盐焗也显示 SGLT-2 抑制剂联合常规降糖药物治疗 T2DM,两组患者不良反应发生率对比无差异,说明达格列净的不良反应较小,在临床中的应用不会增加患者的不良反应,安全性较高。

综上所述,达格列净可显著改善 2 型糖尿病合并稳定性心功能不全患者的血糖、血尿酸水平,还能够改善患者的心脏功能,值得临床借鉴。

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