

doi: 10.13241/j.cnki.pmb.2021.01.017

格列美脲与沙格列汀联合治疗对 2 型糖尿病患者血糖控制、胰岛素抵抗及血脂的影响 *

黄东毅¹ 贺巍¹ 李小露¹ 熊果¹ 张大灿¹ 孙敏²

(1 南方医科大学珠江医院药剂科 广东 广州 510280; 2 南方医科大学珠江医院内分泌科 广东 广州 510280)

摘要 目的:探讨 2 型糖尿病(T2DM)患者经格列美脲联合沙格列汀治疗后的临床效果,并分析其对患者血糖控制、胰岛素抵抗及血脂的影响。**方法:**选取我院 2017 年 4 月~2019 年 4 月期间接收的 88 例 T2DM 患者,按乱数表法将患者分为研究组(n=44,格列美脲联合沙格列汀治疗)、对照组(n=44,沙格列汀治疗)。比较两组患者临床疗效、血糖、胰岛素抵抗及血脂指标,记录两组患者不良反应情况。**结果:**研究组治疗 3 个月后临床总有效率较对照组升高($P<0.05$)。两组患者治疗 3 个月后空腹血糖(FBG)、餐后两小时血糖(2hPBG)、糖化血红蛋白(HbA1c)、胰岛素抵抗指数(HOMA-IR)、总胆固醇(TC)、低密度脂蛋白(LDL-C)、甘油三酯(TG)均下降,且研究组低于对照组($P<0.05$)。两组患者治疗 3 个月后高密度脂蛋白(HDL-C)、空腹胰岛素(FINS)升高,且研究组高于对照组($P<0.05$)。两组不良反应总发生率比较无差异($P>0.05$)。**结论:**T2DM 患者采用格列美脲联合沙格列汀治疗效果确切,可改善机体血脂水平及胰岛素抵抗,控制血糖水平,且用药安全性较好。

关键词:格列美脲;沙格列汀;2 型糖尿病;血糖;胰岛素抵抗;血脂

中图分类号:R587.1 **文献标识码:**A **文章编号:**1673-6273(2021)01-83-04

The Effect of Glimepiride Combined with Saxagliptin on Blood Glucose Control, Insulin Resistance and Blood Lipid in Patients with Type 2 Diabetes Mellitus*

HUANG Dong-yi¹, HE Wei¹, LI Xiao-lu¹, XIONG Guo¹, ZHANG Da-can¹, SUN Min²

(1 Department of Pharmacy, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong, 510280, China;

2 Department of Endocrinology, Zhujiang Hospital of Southern Medical University, Guangzhou, Guangdong, 510280, China)

ABSTRACT Objective: To explore the clinical effect of glimepiride combined with saxagliptin in type 2 diabetes mellitus (T2DM), and analyze its effect on blood glucose control, insulin resistance and blood lipid. **Methods:** 88 patients with T2DM received by our hospital from April 2017 to April 2019 were selected, they were randomly divided into study group (n=44, glimepiride combined with saxagliptin treatment) and control group (n=44, saxagliptin treatment). The clinical efficacy, blood glucose, insulin resistance and blood lipid indexes of the two groups were compared, and the adverse reactions of the two groups were recorded. **Results:** The total clinical effective rate of the study group was higher than that of the control group ($P<0.05$). The fasting blood glucose (FBG), 2 hour postprandial blood glucose (2hPBG), glycosylated hemoglobin (HbA1c), insulin resistance index (HOMA-IR), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and triglyceride (TG) of the two groups all decreased at 3 months after treatment, and those in the study group were lower than those in the control group ($P<0.05$). 3 months after treatment, the levels of high density lipoprotein cholesterol (HDL-C) and fasting insulin (FINS) in the two groups were increased, and those in the study group were higher than those in the control group ($P<0.05$). There was no significant difference in the total incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Glimepiride combined with saxagliptin is effective in the treatment of patients with T2DM, which can improve the body's blood lipid level and insulin resistance, control the blood glucose level, and the drug safety is better.

Key words: Glimepiride; Saxagliptin; Type 2 diabetes mellitus; Blood glucose; Insulin resistance; Blood lipid

Chinese Library Classification(CLC): R587.1 **Document code:** A

Article ID: 1673-6273(2021)01-83-04

前言

我国目前约有 1 亿糖尿病患者,是全球糖尿病患者最多的国家,给我国人民的生活质量和生命健康带来严重影响^[1]。临床

根据胰岛素功能状况可将糖尿病分为 2 型糖尿病 (Type 2 diabetes mellitus, T2DM)和 1 型糖尿病,其中 1 型糖尿病是指胰岛素功能丧失,无法分泌胰岛素,而 T2DM 则是指胰岛功能处于逐步损伤过程,胰岛素分泌不足,我国的糖尿病患者中,约有

* 基金项目:广东省自然科学基金项目(2018A030313967)

作者简介:黄东毅(1985-),本科,药师,研究方向:药剂配伍及临床药物应用,E-mail:gamer@163.com

(收稿日期:2020-04-23 接受日期:2020-05-18)

90%的患者属于 T2DM^[2,3]。现临床针对 T2DM 患者的治疗主要集中于控制血糖,沙格列汀可通过加强周围组织葡萄糖利用度、调节胰岛素分泌等机制发挥良好的降糖效果^[4,5],但单用沙格列汀降糖效果不佳,仍有不少患者存在血糖波动过大的情况。格列美脲为新型磺脲类药物,可提高胰岛素敏感性,具有常规降糖作用^[6,7]。本研究对我院收治的 T2DM 患者给予格列美脲及沙格列汀联合治疗,疗效确切。

1 资料与方法

1.1 基线资料

2017年4月~2019年4月期间,选取我院接收的88例T2DM患者。纳入标准:(1)参考《中国2型糖尿病防治指南(2010年版)》^[8]:空腹血糖(Fasting blood glucose,FBG)≥7.0 mmol/L,或餐后两小时血糖(2 hour postprandial blood glucose,2hPBG)≥11.1 mmol/L;(2)患者或家属签署知情同意书;(3)精神状态良好,意识清晰者。排除标准:(1)治疗前1个月内服用调脂药物者;(2)对本次研究使用药物存在禁忌者;(3)妊娠或哺乳期妇女;(4)合并肝肾功能异常、甲亢、血液疾病及恶性肿瘤者;(5)治疗过程中出现电解质紊乱、酸中毒、心血管疾病者;(6)依从性差,中途退出治疗者;(7)1型糖尿病患者。按乱数表法将患者分为研究组(n=44)、对照组(n=44)。其中对照组男19例,女25例;年龄32~69岁,平均(48.53±4.92)岁;病程2~16年,平均(7.61±2.08)年;体质量指数21.6~27.8 kg/m²,平均(24.28±0.96) kg/m²。研究组男27例,女17例;年龄34~70岁,平均(49.06±5.52)岁;病程2~15年,平均(7.43±1.87)年;体质量指数21.4~26.9 kg/m²,平均(24.51±1.02) kg/m²。两组一般资料比较无显著性差异($P>0.05$)。

1.2 方法

入院后两组给予T2DM相关知识宣教,口服二甲双胍控制血糖水平。在此基础上,对照组给予沙格列汀片(阿斯利康制药有限公司,国药准字J20160069,规格:5 mg)治疗,5 mg/次,

早餐前0.5h口服,1次/d。研究组则在对照组的基础上联合格列美脲片(赛诺菲(北京)制药有限公司,国药准字H20057672,规格:2 mg)治疗,初始剂量2 mg,根据患者病情情况进行调节,最大剂量为6 mg/次,早餐前0.5h口服,1次/d。均治疗3个月。

1.3 观察指标

(1)记录两组临床疗效。疗效判定标准如下^[9]:显效:FBG、2hPBG、糖化血红蛋白(glycosylated hemoglobin,HbA1c)均降低>30%,血脂指标显著改善;有效:FBG、2hPBG、HbA1c均降低10%~30%,血脂指标有所改善;无效:FBG、2hPBG、HbA1c、血脂指标未见改善甚至加重。总有效率=有效率+显效率。(2)记录两组治疗期间不良反应情况。(3)于治疗前、治疗3个月后采集两组患者空腹静脉血5 mL,采用CX9型全自动生化分析仪(美国贝克曼公司)检测^①血糖指标:FPG、2hPBG,^②血脂指标:总胆固醇(Total cholesterol,TC)、高密度脂蛋白(High density lipoprotein cholesterol,HDL-C)、低密度脂蛋白(Low density lipoprotein cholesterol,LDL-C)、甘油三酯(Triglyceride,TG)。采用糖化血红蛋白仪测定HbA1c。(4)于治疗前、治疗3个月后于空腹取患者静脉血3 mL,3800 r/min离心16 min,离心半径10 cm,分离待测。空腹胰岛素水平(Fasting insulin,FINS)采用酶联免疫法测定,并计算胰岛素抵抗指数(HOMA-IR)。其中HOMA-IR = FINS×FPG/22.5。

1.4 统计学方法

采用SPSS21.0进行数据处理,以率表示计数资料,行 χ^2 检验,以($\bar{x}\pm s$)表示计量资料,行t检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 临床疗效比较

与对照组相比较,研究组治疗3个月后临床总有效率升高($P<0.05$),详见表1。

表1 两组临床疗效比较【例(%)】

Table 1 Comparison of clinical effects between the two groups[n(%)]

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group(n=44)	13(29.55)	18(40.91)	13(29.55)	31(70.45)
Study group(n=44)	18(40.91)	22(50.00)	4(9.09)	40(90.91)
χ^2				5.906
P				0.015

2.2 血糖指标比较

两组患者治疗前FBG、2hPBG、HbA1c比较无统计学差异($P>0.05$);两组患者治疗3个月后FBG、2hPBG、HbA1c均下降,且与对照组相比较,研究组下降幅度更大($P<0.05$);详见表2。

2.3 胰岛素抵抗指标比较

两组患者治疗前FINS、HOMA-IR比较无统计学差异($P>0.05$);两组患者治疗3个月后HOMA-IR均下降,FINS均升高,且与对照组相比较,研究组HOMA-IR下降幅度更大,研究组FINS升高幅度更大($P<0.05$);详见表3。

2.4 血脂指标比较

两组患者治疗前TC、HDL-C、LDL-C、TG比较无差异($P>0.05$);两组患者治疗3个月后TC、LDL-C、TG均下降,HDL-C均升高,且与对照组相比较,研究组TC、LDL-C、TG下降幅度更大,研究组HDL-C升高幅度更大($P<0.05$);详见表4。

2.5 不良反应

治疗期间,对照组不良反应总发生率为15.91%(7/44),包括3例头疼、2例恶心、2例呕吐;研究组不良反应总发生率为20.45%(9/44),包括2例头疼、4例恶心、3例呕吐。两组不良反应总发生率比较无差异($\chi^2=0.306$, $P=0.580$)。

表 2 两组血糖指标比较($\bar{x} \pm s$)Table 2 Comparison of blood glucose indexes between the two groups($\bar{x} \pm s$)

Groups	FBG(mmol/L)		2hPBG(mmol/L)		HbA1c(%)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=44)	9.62±0.91	7.93±1.16*	13.34±1.39	9.67±1.25*	11.96±1.65	8.80±1.67*
Study group(n=44)	9.51±0.87	6.11±0.82*	13.21±1.26	7.23±1.04*	11.67±1.49	6.34±1.19*
t	0.580	8.498	0.460	9.954	0.865	7.958
P	0.564	0.000	0.647	0.000	0.389	0.000

Note: compared with before treatment, * $P < 0.05$.表 3 两组胰岛素抵抗指标比较($\bar{x} \pm s$)Table 3 Comparison of insulin resistance indexes between the two groups($\bar{x} \pm s$)

Groups	FINS(μ U/mL)		HOMA-IR(%)	
	Before treatment	After treatment	Before treatment	After treatment
Control group(n=44)	9.61±0.92	13.63±1.83*	4.82±0.73	3.26±0.52*
Study group(n=44)	9.53±0.88	17.19±1.61*	4.75±0.64	2.07±0.47*
t	0.417	9.688	0.478	11.262
P	0.678	0.000	0.634	0.000

Note: compared with before treatment, * $P < 0.05$.表 4 两组血脂指标比较($\bar{x} \pm s$, mmol/L)Table 4 Comparison of blood lipid indexes between the two groups($\bar{x} \pm s$, mmol/L)

Groups	TC		HDL-C		LDL-C		TG	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group(n=44)	6.22±1.04	4.82±1.15*	1.14±0.22	1.57±0.29*	4.58±0.91	3.01±0.59*	4.08±0.93	2.94±0.81*
Study group(n=44)	6.13±1.15	3.09±1.07*	1.19±0.16	1.96±0.21*	4.67±0.73	1.63±0.42*	4.01±0.84	1.32±0.75*
t	0.385	7.306	1.219	7.225	0.512	12.640	0.371	9.734
P	0.701	0.000	0.216	0.000	0.610	0.000	0.712	0.000

Note: compared with before treatment, * $P < 0.05$.

3 讨论

T2DM 是内分泌科的常见病和多发病,以慢性高血糖为主要病理表现,是遗传、环境等多因素作用的结果^[10]。经流行病学报告显示^[11],我国 T2DM 的患病率日益递增,成年 T2DM 患者已经占比 9.7%。且若患者长期处于高血糖的刺激下,同时其还伴随着血脂的异常,可引起各靶器官损害,引发多种并发症危及患者生命^[12,13]。现临床有关 T2DM 的治疗尚无根治性方案,多采用二甲双胍、磺脲类、DPP-4 抑制剂及胰岛素等降糖药物进行对症降糖治疗,但上述药物单用降糖效果一般,且 T2DM 患者治疗的周期较长,需要持续给予降糖治疗,患者耐受性降低^[14]。故临床治疗时多采取联合用药方案,合理的治疗方案的宗旨在于不仅要控制血糖,还应尽可能地减少不良反应的发生率。沙格列汀属于肠促胰素的降糖药物,可使肠促胰素作用时间延长,进而控制血糖^[15,16]。格列美脲适用于单纯饮食控制和锻炼未能控制血糖的 T2DM 患者^[17,18]。

本次研究结果显示,治疗 3 个月后,研究组的临床疗效、血糖指标均优于对照组,可见 T2DM 患者经格列美脲联合沙格

列汀治疗后,血糖水平控制良好,疗效显著。分析其原因,人体进食后肠道内会分泌胰高血糖素样肽-1,并刺激胰岛分泌胰岛素,但二肽基肽酶-4 可加速胰高血糖素样肽-1 的分解,导致胰岛素分泌不足,无法稳定血糖水平,而二肽基肽酶-4 抑制剂如沙格列汀可抑制二肽基肽酶-4 的产生,减轻其对胰高血糖素样肽-1 的刺激,显著降低血糖水平^[19-21]。格列美脲是一种长效抗糖尿病药,其降糖的主要机制在于:格列美脲可与胰腺 β -细胞表面的受体结合,增加机体胰岛素的释放,促进钙离子内流,同时还可抑制肝葡萄糖的合成^[22-24]。两种药物从不同的降糖机制出发,发挥良好的协同作用。本次研究结果还显示,治疗 3 个月后,研究组的胰岛素抵抗改善效果更佳,这可能是由于格列美脲进入人体后和磺脲类受体 65kda 亚单位结合,可迅速解离及结合,提高葡萄糖的运转,并促进外周肌肉、脂肪组织对葡萄糖的吸收,以此改善胰岛素抵抗情况^[25-27]。此外,两组患者治疗后 TC、LDL-C、TG、HDL-C 均有所改善,且格列美脲联合沙格列汀治疗者改善效果更佳。我们分析,可能主要是以下几个原因:一是因为联合用药可改善患者内分泌紊乱及血糖,确保机体内环境稳定,进而改善血脂水平。二是因为格列美脲可降低

空腹及餐时相关非酯化脂肪酸的水平,进而降低 TG 水平。另两组的安全性均较好,不良反应总发生率差异不明显。由于受样本量、研究时间限制,本次研究结果可能存在一定的偏倚,后续报道将增加随访时间、扩大样本量以获取更为准确的数据。

综上所述,T2DM 患者经格列美脲联合沙格列汀治疗后,血糖水平控制效果较佳,可有效改善机体血脂及胰岛素抵抗,疗效确切,且用药安全性较好,临床应用价值较高。

参考文献(References)

- [1] 汪会琴,胡如英,武海滨,等. 2 型糖尿病报告发病率研究进展[J]. 浙江预防医学, 2016, 28(1): 37-39, 57
- [2] Tai H, Jiang XL, Kuang JS, et al. Longitudinal follow-up study of the retrobulbar and intrarenal hemodynamics in patients with T2DM[J]. Medicine (Baltimore), 2019, 98(46): e17792
- [3] 陈红霞,史婷婷,袁群,等. 吡格列酮联合阿卡波糖对 2 型糖尿病患者血清 RBP4、Leptin、Visfatin 水平的影响 [J]. 现代生物医学进展, 2018, 18(21): 4152-4155, 4121
- [4] Franco DR, Perez-Nieves M, Ivanova JI, et al. Basal insulin persistence in Brazilian participants with T2DM[J]. Rev Assoc Med Bras (1992), 2019, 65(10): 1254-1264
- [5] 孙玥,李英,王敏哲,等. 沙格列汀联合二甲双胍治疗初诊 2 型糖尿病患者的疗效[J]. 中国老年学杂志, 2014, 34(15): 4172-4173
- [6] Jiang J, She X, Zhu J, et al. A composite consisting of sulfo-functionalized magnetic graphene and mesoporous silica for extraction of metformin and glimepiride prior to their determination by liquid chromatography tandem mass spectrometry [J]. Mikrochim Acta, 2019, 186(8): 590
- [7] Mokta JK, Ramesh, Sahai AK, et al. Comparison of Safety and Efficacy of Glimepiride-Metformin and Vildagliptin- Metformin Treatment in Newly Diagnosed Type 2 Diabetic Patients [J]. J Assoc Physicians India, 2018, 66(8): 30-35
- [8] 中华医学会糖尿病学分会. 中国 2 型糖尿病防治指南 (2010 年版) [J]. 中国糖尿病杂志, 2012, 20(1): 后插 1- 后插 36
- [9] 徐丹,黄龙贤,周大燕,等. 瑞格列奈分别联合氨氯地平、氯沙坦钾治疗 T2DM 合并原发性高血压的疗效和安全性比较 [J]. 中国药房, 2017, 28(3): 327-330
- [10] Parisi EJ, Baggish AL. Exercise and Cardiovascular Risk among Masters Athletes with Type 2 Diabetes [J]. Curr Diab Rep, 2019, 19 (11): 127
- [11] 段发兰,李亚新,杜良琴,等. 2 型糖尿病患者血糖和胰抑素 C 水平与肾脏早期病变的关系[J]. 检验医学与临床, 2011, 8(2): 199-201
- [12] McCoy MA, Theeke LA. A systematic review of the relationships among psychosocial factors and coping in adults with type 2 diabetes mellitus[J]. Int J Nurs Sci, 2019, 6(4): 468-477
- [13] Ezema CI, Omeh E, Onyeso OKK, et al. The Effect of an Aerobic Exercise Programme on Blood Glucose Level, Cardiovascular Parameters, Peripheral Oxygen Saturation, and Body Mass Index among Southern Nigerians with Type 2 Diabetes Mellitus, Undergoing Concurrent Sulfonylurea and Metformin Treatment [J]. Malays J Med Sci, 2019, 26(5): 88-97
- [14] Okada J, Yamada E, Nijima Y, et al. Comparison of serum amylase level between dipeptidyl peptidase-4 inhibitor and GLP-1 analog administration in patients with type 2 diabetes mellitus [J]. J Health Popul Nutr, 2019, 38(1): 33
- [15] Chen Q, Liu T, Zhou H, et al. Risk of Fractures Associated with Dipeptidyl Peptidase-4 Inhibitor Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials [J]. Diabetes Ther, 2019, 10(5): 1879-1892
- [16] Strain WD, McEwan P, Howitt H, et al. Retrospective Database Analysis Evaluating the Clinical Outcomes of Changing Treatment of People with Type 2 Diabetes Mellitus (T2DM) from Other DPP-4 Inhibitor Therapy to Alogliptin in a Primary Care Setting[J]. Diabetes Ther, 2019, 10(4): 1499-1507
- [17] 蒲丹岚,尹经霞,谢洁,等. 复方盐酸吡格列酮格列美脲片与格列美脲片治疗 2 型糖尿病的疗效与安全性对照研究 [J]. 重庆医学, 2018, 47(7): 915-918
- [18] Ebid AIM, Ehab M, Ismail A, et al. The influence of SLC22A1 rs622342 and ABC8 rs757110 genetic variants on the efficacy of metformin and glimepiride combination therapy in Egyptian patients with type 2 diabetes[J]. J Drug Assess, 2019, 8(1): 115-121
- [19] Ishii H, Suzaki Y, Miyata Y, et al. Randomized Multicenter Evaluation of Quality of Life and Treatment Satisfaction in Type 2 Diabetes Patients Receiving Once-Weekly Trelagliptin Versus a Daily Dipeptidyl Peptidase-4 Inhibitor [J]. Diabetes Ther, 2019, 10 (4): 1369-1380
- [20] Esaki H, Tachi T, Goto C, et al. Relationship Between Initial Renal Function and the Inhibitory Effect of Dipeptidyl Peptidase-4 Inhibitor Treatment on Renal Function Decline [J]. Pharmazie, 2019, 74 (6): 374-382
- [21] Kim HJ, Kim YS, Lee CB, et al. Efficacy and Safety of Switching to Tenoeligliptin in Patients with Type 2 Diabetes Inadequately Controlled with Dipeptidyl Peptidase-4 Inhibitors: A 12-Week Interim Report[J]. Diabetes Ther, 2019, 10(4): 1271-1282
- [22] Park JW, Kim KA, Choi YJ, et al. Effect of glimepiride on the pharmacokinetics of teneligliptin in healthy Korean subjects[J]. J Clin Pharm Ther, 2019, 44(5): 720-725
- [23] Hussain M, Rafique MA, Iqbal J, et al. Effect of sitagliptin and glimepiride on C-reactive protein (CRP) in overweight Type-2 diabetic patients[J]. Pak J Med Sci, 2019, 35(2): 383-387
- [24] Tandon T, Dubey AK, Srivastava S, et al. A pharmacoeconomic analysis to compare cost-effectiveness of metformin plus teneligliptin with metformin plus glimepiride in patients of type-2 diabetes mellitus[J]. J Family Med Prim Care, 2019, 8(3): 955-959
- [25] Nyström T, Santos-Pardo I, Fang X, et al. Heart rate variability in type 2 diabetic subjects randomized to liraglutide or glimepiride treatment, both in combination with metformin: A randomized, open, parallel-group study [J]. Endocrinol Diabetes Metab, 2019, 2 (2): e00058
- [26] Cruz-Angeles J, Videia M, Martínez LM. Highly Soluble Glimepiride and Irbesartan Co-amorphous Formulation with Potential Application in Combination Therapy[J]. AAPS PharmSciTech, 2019, 20(4): 144
- [27] DeFronzo RA, Ferrannini E, Scherthaner G, et al. Slope of change in HbA1c from baseline with empagliflozin compared with sitagliptin or glimepiride in patients with type 2 diabetes [J]. Endocrinol Diabetes Metab, 2018, 1(2): e00016