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沙格列汀联合二甲双胍治疗 2 型糖尿病合并脑梗死的临床疗效

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[摘　要]　**目的：**观察沙格列汀联合二甲双胍治疗2型糖尿病(type 2 diabetes mellitus，T2DM)合并脑梗死的临床疗效。**方法：**选择2018年9月至2020年6月于徐州医科大学附属医院内分泌科住院的T2DM合并脑梗死的患者139例，将上述患者随机分为2组，A组接受沙格列汀联合二甲双胍治疗，B组接受格列美脲片治疗。2组患者连续治疗12周，比较治疗前后血糖、中性粒细胞计数与淋巴细胞计数的比值(neutrophil-to-lymphocyte ratio，NLR)、血小板计数与淋巴细胞计数的比值(platelet-to-lymphocyte ratio，PLR)、血糖波动指标、颈动脉内膜中层厚度(carotid intima-media thickness，CIMT)。**结果：**治疗12周后，2组空腹血糖(fasting blood glucose，FBG)、餐后2 h血糖(2-h postprandial blood glucose，2hPG)、糖化血红蛋白(glycosylated hemoglobin A1c，HbA1c)均较治疗前明显降低(P<0.05)，且A组较B组下降更明显(P<0.05)。A组NLR及PLR较治疗前明显降低(P<0.05)，B组NLR和PLR较治疗前无明显变化(P>0.05)。2组血糖水平的标准差(standard deviation of the blood glucose concentrations，SDBG)、餐后血糖波动幅度(postprandial glucose excursions，PPGE)、最大血糖波动幅度(largest amplitude of glycemic excursions，LAGE)均较治疗前明显下降(P<0.05)，且A组较B组下降更明显(P<0.05)。A组CIMT较治疗前降低(P<0.05)，B组CIMT较治疗前降低，但差异无统计学意义(P>0.05)，组间比较差异有统计学意义(P<0.05)。**结论：**沙格列汀联合二甲双胍治疗T2DM合并脑梗死能有效改善患者的血糖波动、NLR和PLR，改善由高血糖导致的动脉粥样硬化程度，值得临床推广。

[关键词]　2型糖尿病；脑梗死；沙格列汀；中性粒细胞计数与淋巴细胞计数的比值；血小板计数与淋巴细胞计数的比值；血糖波动

Clinical efficacy of saxagliptin combined with metformin in the treatment of type 2 diabetes mellitus complicated with cerebral infarction

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Abstract　**Objective:** To observe the clinical efficacy of saxagliptin combined with metformin in the treatment of type 2

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diabetes mellitus (T2DM) complicated with cerebral infarction. **Methods:** The clinical data of 139 patients with T2DM complicated with cerebral infarction in the Department of Endocrinology, Affiliated Hospital of Xuzhou Medical University from September 2018 to June 2020 were analyzed retrospectively. They were randomly divided into two groups: group A received saxagliptin combined with metformin and group B received glimepiride. Blood glucose, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), blood glucose fluctuation, and carotid intima-media thickness (CIMT) were compared between the two groups before and after the treatment (12 weeks). **Results:** After 12 weeks of treatment, fasting blood glucose (FBG), 2-h postprandial blood glucose (2hPG), and glycosylated hemoglobin A1c (HbA1c) in both groups were significantly lower than those before the treatment (P<0.05), and the decline in group A was more pronounced than that in group B (P<0.05). The NLR and PLR of group A were significantly decreased compared with that before the treatment (P<0.05), while the NLR and PLR of group B had no significant changes compared with that before the treatment (P>0.05). The standard deviation of the blood glucose concentrations (SDBG), postprandial glucose excursions (PPGE) and largest amplitude of glycemic excursions (LAGE) were all significantly lower than those before the treatment (P<0.05), and the decline in group A was more pronounced than that in group B (P<0.05). CIMT in group A was lower than that before the treatment (P<0.05) and CIMT in group B was also lower than that before the treatment, but the difference was not statistically significant (P>0.05), and the difference between groups was statistically significant (P<0.05). **Conclusion:** Saxagliptin combined with metformin in the treatment of T2DM complicated with cerebral infarction is a safe and effective therapy for the improvement of the blood glucose fluctuation, NLR, PLR, and the degree of atherosclerosis generated by hyperglycemia. It is worthy of clinical application and promotion.

Keywords type 2 diabetes mellitus; cerebral infarction; saxagliptin; neutrophil-to-lymphocyte ratio; platelet-to-lymphocyte ratio; blood glucose fluctuation

2型糖尿病(type 2 diabetes mellitus，T2DM)是最常见的代谢性疾病，在疾病进展过程中可导致大血管、小血管及微血管损伤，进一步可发展为冠心病及脑梗死，其致残率及致死率可高达70%[1-3]。流行病学显示高血糖是脑梗死的独立危险因素，需要引起足够的重视[4]。沙格列汀(saxagliptin)是二肽基肽酶-4抑制剂(dipeptidyl peptidase 4，DPP-4)，可维持和延长促胰岛激素(glucagon-like peptide 1，GLP-1)的存在时间和活性，从而降低血糖。研究[5]证实沙格列汀可有效降低糖尿病患者心脑血管的发生率。作为T2DM的一线治疗药物，二甲双胍(metformin)具有促进葡萄糖吸收，抑制糖异生的作用[6]。格列美脲为第3代磺酰脲类长效抗糖尿病药物，因其成本低，降糖效果好，在临床实践中被广泛应用。目前，临床上关于沙格列汀联合二甲双胍或格列美脲用于治疗T2DM合并脑梗死的相关研究较少。因此，笔者以格列美脲为对照，选取T2DM合并脑梗死患者进行比较分析，旨在研究沙格列汀联合二甲双胍治疗的临床疗效。

1 对象与方法

1.1 对象

选择2018年9月至2020年4月于徐州医科大学附属医院内分泌科住院的T2DM合并脑梗死的患者139例，其中男79例，女60例，年龄(63.23±9.35)岁，T2DM诊断标准符合1999年WHO糖尿病诊断标准，脑梗死的诊断标准符合2007年中国脑血管病防治指南编写委员会制定的《中国脑血管病防治指南》中关于脑梗死的诊断标准。纳入标准：1)年龄18~80岁；2)血糖控制欠佳，糖化血红蛋白(glycosylated hemoglobin A1c，HbA1c)为7.0%~15.5%。排除标准：1)1型糖尿病；2)对本研究药物过敏及有严重不良反应；3)糖尿病急性并发症；4)严重心血管、肝、肾疾病及感染性疾病；5)哺乳期或妊娠期妇女；6)血液系统疾病及恶心肿瘤。将最终纳入的患者分为2组，其中A组(沙格列汀+二甲双胍)70例，男41例，女29例，年龄(63.46±8.81)岁；B组(格列美脲片)69例，男38例，女31例，年龄(63.00±9.93)岁。

1.2 方法

患者均接受糖尿病健康教育。A组患者予以沙格列汀(安立泽，AstraZeneca Pharmaceuticals LP)5 mg口服，每天1次。二甲双胍(格华止，中美上海施贵宝制药有限公司)0.5 g口服，每天2次；B组应用格列美脲片(亚莫利，赛诺菲-安万特公司)2 mg口服，每次1~2 mg，每天2~3次。2组患者均持续治疗12周。分别于治疗前及治疗12周后采集患者空腹的静脉血5 mL。

1.3 观察指标

1.3.1 一般资料

收集患者的一般资料，包括性别、年龄、身高、体重、吸烟史、饮酒史、病程、糖尿病家族史、高血压病史、高脂血症病史，并计算体重指数(body mass index，BMI)。患者在仰卧位休息至少5 min后，在主臂上使用水银血压计测量血压。患者的手臂置于心脏水平，血压值取3次测量的平均值。

1.3.2 血糖、NLR、PLR

入组患者过夜禁食8~12 h，次日清晨采集肘静脉血，分离血清。采用全自动生化分析(日本奥林巴斯公司，日立7600)检测空腹血糖(fasting blood glucose，FBG)、餐后2 h血糖(2-h postprandial blood glucose，2hPG)。采用全自动糖化血红蛋白分析仪(瑞士罗氏公司)检测HbA1c。采用LH755型自动血液分析仪(贝克曼库尔特公司)检测中性粒细胞(neutrophil count，NE)和淋巴细胞计数(lymphocyte count，L)，并计算中性粒细胞计数与淋巴细胞计数的比值(neutrophil-to-lymphocyte ratio，NLR)及血小板计数(platelet，PLT)与淋巴细胞计数的比值(platelet-to-lymphocyte ratio，PLR)。

1.3.3 血糖波动指标

患者在不改变降糖方案和饮食、运动的生活方式下进行“7个点”(早、午、晚三餐前，三餐后 2 h及睡前血糖)的自我血糖监测(self-monitoring of blood glucose，SMBG)。1)血糖水平的标准差(standard deviation of the blood glucose concentrations，SDBG)：1 d内多点血糖的标准差。2)餐后血糖波动幅度(postprandial glucose excursions，PPGE)：三餐后2 h的血糖与其相应餐前血糖差值绝对值的平均值。3)最大血糖波动幅度(largest amplitude of glycemic excursions，LAGE)：日内最大和最小血糖值之差。

1.3.4 超声测量

采用美国PHILIPS IE33多功能彩超诊断仪测量内膜中层厚度(carotid intima-media thickness，CIMT)，从颈总动脉近端至远端、横切和纵切自下而上连续扫查，每位患者连续测量3次，双侧取平均值。

1.4 统计学处理

采用SPSS 22.0统计学软件进行数据分析。计量资料以均数±标准差($\bar{x}\pm s$)表示，组间比较采用两独立样本t检验，治疗前后比较采用配对t检验。计数资料以例(%)表示，比较采用χ^2检验。P<0.05为差异有统计学意义。

2 结果

2.1 一般资料

治疗前两组患者性别、年龄、BMI、平均动脉压、吸烟史、饮酒史、糖尿病病程、糖尿病家族史、高血压病史、高脂血症病史，NE、L、PLT、NLR、PLR、FPG、2hPG、HbA1c、血糖波动指标、CIMT均无明显差异(均P>0.05；表1，图1)，具有可比性。

2.2 2组血糖、NLR、PLR

治疗12周后，2组的FBG、2hPG、HbA1c均较治疗前均明显降低(均P<0.05)，A组NLR和PLR较治疗前均明显降低(均P<0.05)，B组NLR和PLR较治疗前均无明显变化(均P>0.05，表2)。

2.3 2组血糖波动指标比较

治疗12周后，2组SDBG、PPGE、LAGE均较治疗前均明显下降(均P<0.05)，且A组较B组下降更明显(P<0.05，表3)。

2.4 2组 CIMT 指标比较

治疗12周后，A组CIMT较治疗前降低(P<0.05)，B组CIMT较治疗前降低，但差异无统计学意义(P>0.05)。组间比较差异有统计学意义(P<0.05，表3)。

表1 2组患者一般资料比较

Table 1 Comparison of general data of the patients in 2 groups

指标	A组(n=70)	B组(n=69)	χ^2/t	P
性别(男/女)/例	41/29	38/31	0.173	0.677
年龄/岁	63.46 ± 8.81	63.00 ± 9.93	−0.287	0.774
BMI/(kg·m^{-2})	25.73 ± 2.74	24.92 ± 2.82	−1.716	0.088
平均动脉压/mmHg	105.51 ± 15.43	104.00 ± 16.70	−0.555	0.580
糖尿病病程/年	10.86 ± 7.22	11.08 ± 7.30	−0.181	0.857
吸烟史/[例(%)]	12 (17.1)	16 (23.2)	0.790	0.374
饮酒史/[例(%)]	11 (15.7)	14 (20.3)	0.493	0.483
糖尿病家族史/[例(%)]	9 (12.9)	6 (8.7)	0.625	0.429
高血压病史/[例(%)]	36 (51.4)	35 (50.7)	0.007	0.934
高脂血症病史/[例(%)]	0 (0.0)	1 (1.4)	1.022	0.496
NE/($\times 10^9$·L^{-1})	3.93 ± 1.16	4.03 ± 1.25	0.486	0.628
L/($\times 10^9$·L^{-1})	1.93 ± 0.55	1.99 ± 0.62	0.631	0.529
PLT/($\times 10^9$·L^{-1})	213.66 ± 45.32	214.35 ± 50.00	0.085	0.932
NLR	2.147 ± 0.701	2.168 ± 0.890	0.153	0.879
PLR	119.085 ± 41.587	114.775 ± 36.122	−0.652	0.516
FBG/(mmol·L^{-1})	8.57 ± 2.46	8.82 ± 3.54	0.491	0.624
2hPG/(mmol·L^{-1})	19.52 ± 3.92	19.14 ± 4.74	−0.515	0.608
HbA1c/%	9.17 ± 1.37	9.31 ± 1.74	0.511	0.611
SDBG/(mmol·L^{-1})	4.60 ± 1.59	4.52 ± 1.65	−0.312	0.755
PPGE/(mmol·L^{-1})	5.94 ± 1.52	5.87 ± 1.59	−0.265	0.792
LAGE/(mmol·L^{-1})	5.77 ± 1.49	5.71 ± 1.52	−0.229	0.819
CIMT/mm	1.31 ± 0.12	1.32 ± 0.09	0.980	0.329

1 mmHg=0.133 kPa.

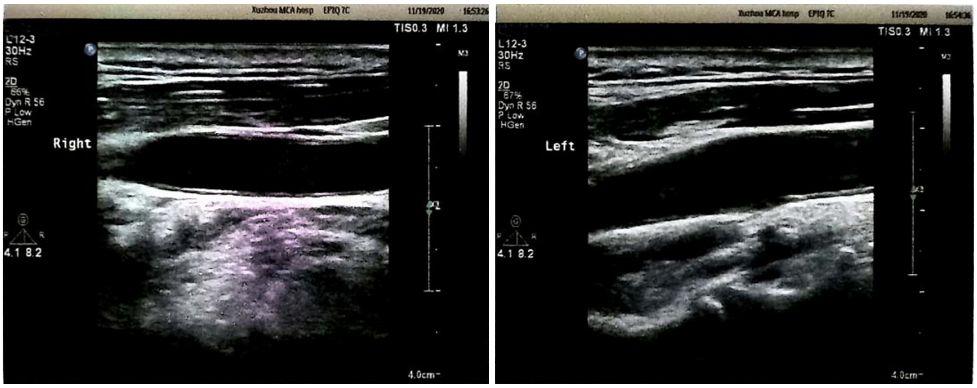

图1 T2DM合并脑梗死患者的颈部血管彩超

Figure 1 Neck vascular color ultrasound in patients with T2DM patients complicated with cerebral infarction

表2 2组患者治疗前后血糖、NLR、PLR比较

Table 2 Comparison of blood glucose, NLR, and PLR before and after the treatment between the 2 groups

指标	A组(n=70)				B组(n=60)				治疗后组间比较	
	治疗前	治疗后	t	P	治疗前	治疗后	t	P	t	P
FBG	8.57 ± 2.46	6.45 ± 0.98	9.937/	<0.001	8.82 ± 3.54	7.09 ± 1.79	6.893	<0.001	−2.643	0.009
2hPG	19.52 ± 3.92	11.08 ± 1.62	20.633	<0.001	19.14 ± 4.74	13.36 ± 3.07	14.347	<0.001	−5.469	<0.001
HbA1c	9.17 ± 1.37	7.23 ± 0.68	15.093	<0.001	9.31 ± 1.74	8.05 ± 1.16	9.948	<0.001	−5.101	<0.001
NLR	2.147 ± 0.701	1.82 ± 0.56	10.839	<0.001	2.168 ± 0.890	2.169 ± 0.857	−0.018	0.986	−2.852	0.005
PLR	119.085 ± 41.587	104.34 ± 34.169	9.094	<0.001	114.775 ± 36.122	113.626 ± 33.612	0.539	0.592	−1.615	0.109

表3 2组患者治疗前后血糖波动、CIMT指标比较

Table 3 Comparison of blood glucose fluctuation and CIMT parameters between the 2 groups before and after the treatment

组别	SDBG/(mmol·L^{-1})	PPGE/(mmol·L^{-1})	LAGE/(mmol·L^{-1})	CIMT/(mmol·L^{-1})
A组(n=70)				
治疗前	4.60 ± 1.59	5.94 ± 1.52	5.77 ± 1.49	1.31 ± 0.12
治疗后	3.69 ± 1.25	4.66 ± 0.97	4.74 ± 1.01	1.15 ± 0.10
t	9.621	12.362	11.251	13.442
P	<0.001	<0.001	<0.001	<0.001
B组(n=60)				
治疗前	4.52 ± 1.65	5.87 ± 1.59	5.71 ± 1.52	1.32 ± 0.09
治疗后	4.202 ± 1.614	5.383 ± 1.406	5.474 ± 1.504	1.31 ± 0.09
t	10.490	7.936	9.967	1.946
P	<0.001	<0.001	<0.001	0.056
治疗后组间比较				
t	−2.072	−3.545	−3.372	−10.002
P	0.004	0.001	0.001	<0.001

3 讨论

随着社会经济的发展，我国的T2DM的患病率呈快速上升趋势[7]，尤其是糖尿病大血管病变已经成为影响糖尿病患者寿命的主要原因。脑梗死作为糖尿病合并大血管并发症之一，具有医疗费用高、预后差、致残高、致死率高的特点。因此，对于糖尿病合并脑梗死患者的治疗，临床医生面临着严峻的挑战。

GLP-1是由肠道L细胞合成分泌的肠促胰素，有葡萄糖依赖性促胰岛素分泌的特性，但天然的GLP-1半衰期短，在1~2 min内被机体内DPP-4裂解。沙格列汀具有抑制DPP-4的活性，延长GLP-1活性的特点，目前已经被广泛应用于临床。二甲双胍是治疗糖尿病的一线用药，不仅能通过改善高血糖、胰岛素抵抗及动脉粥样硬化以改善体内的慢性炎症，还具有直接抗炎的作用[8]。格列美脲为磺脲类降糖药物，能够快速与磺酰脲受体特异性结合来刺激胰岛β细胞，从而增加胰岛素的分泌，发挥控制血糖的作用。

糖尿病患者机体长期处于一种慢性低度炎症状态，当发生脑梗死时，体内的炎症反应会更加强烈，血液中的中性粒细胞计数会持续升高[9]。国内已有研究[10]证实脑梗死面积的大小和神经功能的恢复与中性粒细胞计数密切相关。NLR和PLR作为新兴的炎症指标，在临床实践当中更加稳定且

较易获取，其与动脉粥样硬化、糖尿病及糖尿病慢性并发症如糖尿病视网膜病变、糖尿病肾病、糖尿病合并冠心病、糖尿病合并脑梗死具有密切联系[11-16]。CIMT增厚是早期动脉粥样硬化的标志，也是发生卒中风险重要的决定因素。本研究证实沙格列汀联合二甲双胍治疗可使T2DM患者血糖下降，NLR、LPR、CIMT明显下降；说明沙格列汀联合二甲双胍除了和格列美脲同样的降糖作用以外，还能够控制机体的氧化应激水平，防止破坏细胞，保护机体血管等重要系统[17]。众所周知，氧化应激和机体内细胞功能异常有关，氧自由基的增多会导致细胞和血管内皮的损伤，从而引起机体严重的炎性反应和动脉粥样硬化。

血糖波动是指机体的血糖水平在一定时间内在峰值与谷值之间波动的情况，是不同于HbA1c的糖尿病评价指标，血糖波动较大可导致血管内皮功能紊乱，凝血系统、纤溶系统功能障碍，从而促进脑血管疾病的发生发展[18-19]。血糖波动与糖尿病大血管并发症密切相关[20]。本研究结果显示：经12周的治疗后，SDBG、PPGE、LAGE较治疗前降低。这表明沙格列汀联合二甲双胍和单用格列美脲均可有效地控制血糖波动，但前者较后者作用更加明显。因此，沙格列汀联合二甲双胍治疗T2DM合并脑梗死患者，具体良好的治疗效果，不仅能够通过葡萄糖依赖性促胰岛素分泌的特性，显著降低餐后胰高血糖素的分泌水平，增强胰岛素敏感性，降低患者高胰岛素血症等不良事件的发生，还能促进机体外周葡萄糖的摄取和利用，抑制肝糖原异生，改善胰岛素抵抗。

本研究存在一些不足：首先，样本量较少，且为回顾性研究，可能需要大样本的前瞻性研究进一步证实我们的结论。其次，研究对象为徐州地区的T2DM患者，可能存在选择偏倚。

综上所述，沙格列汀联合二甲双胍治疗T2DM合并脑梗死的患者，可有效改善其血糖波动，改善体内的炎症反应，改善由高血糖导致的动脉粥样硬化，说明沙格列汀联合二甲双胍治疗T2DM合并脑梗死是一种有效的治疗方案。

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