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论著·临床

度拉糖肽联合达格列净对早期糖尿病肾病尿蛋白排泄率及血清炎性因子的影响

邢建东, 姚艳琴, 王静茹, 马春明, 陈海丽, 李银玉

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作者单位: 037000 山西省大同市第五人民医院内分泌科(邢建东、王静茹、马春明、陈海丽、李银玉) 影像科(姚艳琴)

通信作者: 邢建东 E-mail: xzokie@163.com

【摘要】目的 观察度拉糖肽联合达格列净对早期糖尿病肾病尿蛋白排泄率及血清炎性因子的影响。方法 选取 2021 年 1—10 月山西省大同市第五人民医院内分泌科诊治早期糖尿病肾病患者 120 例,按随机数字表法分为对照组和观察组,各 60 例。对照组患者给予达格列净治疗,观察组患者在对照组的基础上加用度拉糖肽治疗。比较 2 组患者治疗前后肾功能[肾小球滤过率(GFR)、尿素氮(BUN)、尿酸(UA)及尿蛋白排泄率]、炎性因子水平[转化生长因子- β_1 (TGF- β_1)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)],血糖水平[餐后 2 h 血糖(2 hPG)、空腹血糖(FPG)、糖化血红蛋白(HbA_{1c})],血脂水平[总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)及高密度脂蛋白胆固醇(HDL-C)],以及不良反应发生率。结果 与治疗前比较,治疗后 2 组 BUN、UA、尿蛋白排泄率均降低, GFR 均升高,且观察组改善优于对照组($t=6.215, 20.742, 8.955, 12.431, P$ 均 <0.001);治疗后 2 组血清 TGF- β_1 、IL-6、TNF- α 均降低,且观察组低于对照组($t=12.139, 18.351, 13.889, P$ 均 <0.001);治疗后 2 组餐后 2 h 血糖、空腹血糖、糖化血红蛋白水平均降低,且观察组低于对照组($t=6.835, 8.849, 5.425, P$ 均 <0.001);治疗后 2 组血清 TC、TG、LDL-C 均降低,观察组 HDL-C 升高,且观察组改善优于对照组($t=4.225, 15.746, 4.243, 4.121, P$ 均 <0.001);2 组患者不良反应发生率比较,差异无统计学意义($P>0.05$)。结论 在达格列净治疗的基础上增加度拉糖肽,能有效减轻早期糖尿病肾病患者炎症反应,改善患者肾功能,调节血糖、血脂,且安全有效。

【关键词】糖尿病肾病;达格列净;度拉糖肽;替米沙坦;尿蛋白排泄率;炎性因子

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Effect of dulaglutide combined with dapagliflozin on urinary protein excretion rate and serum inflammatory factors in patients with early diabetic nephropathy Xing Jiandong*, Yao Yanqin, Wang Jingru, Ma Chunming, Chen Haili, Li Yinyu. * Department of Endocrinology, the Fifth People's Hospital of Datong, Shanxi Province, Datong 037000, China

Corresponding author: Xing Jiandong, E-mail: xzokie@163.com

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【Abstract】Objective To observe the effect of dulaglutide combined with dapagliflozin on urinary protein excretion rate and serum inflammatory factors in patients with early diabetic nephropathy. Methods From January to October 2021, 120 patients with early diabetic nephropathy diagnosed and treated by the Department of Endocrinology of the Fifth People's Hospital of Datong, Shanxi Province, were selected and divided into the control group and the observation group according to the random number table method, with 60 patients in each group. The patients in the control group were treated with dapagliflozin combined with telmisartan, and the patients in the observation group were treated with dulaglutide on the basis of the control group. The renal function [glomerular filtration rate (GFR), urea nitrogen (BUN), uric acid (UA) and urinary protein excretion rate] and the level of inflammatory factors [transforming growth factor- β_1 (TGF- β_1), interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α)], Blood glucose level (2h postprandial blood glucose, fasting blood glucose, glycosylated hemoglobin), blood lipid level [total cholesterol (TC), triacylglycerol (TG), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C)] were compared between the two groups before and after treatment, and the incidence of adverse reactions. Results Compared with that before treatment, the excretion rates of BUN, UA, GFR and urinary protein in the two groups decreased after treatment, but the excretion rates of BUN, UA and urinary protein in the observation group were lower than those in the control group, and GFR was higher than those in the control group ($t=6.215, 20.742, 8.955, 12.431, P$ <

0.001)。Serum TGF- β_1 , IL-6, TNF- α of the two groups after treatment was lower in the observation group than in the control group ($t=12.139, 18.351, 13.889, P<0.001$)。After treatment, the levels of blood glucose, fasting blood glucose and glycosylated hemoglobin at 2h after meal in both groups decreased, and those in the observation group were lower than those in the control group ($t=6.835, 8.849, 5.425, P<0.001$)。After treatment, serum TC, TG, LDL-C in both groups decreased, HDL-C in the observation group increased, and the improvement in the observation group was better than that in the control group ($t=4.225, 15.746, 4.243, 4.121, P<0.001$)。There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$)。 **Conclusion** On the basis of treatment with dagelin combined with telmisartan, the addition of dulaglutide can effectively reduce the level of serum inflammatory factors and urinary protein excretion rate in patients with early diabetic nephropathy, reduce inflammatory reaction, improve renal function, regulate blood sugar, and is safe and effective.

【Key words】 Diabetic nephropathy; Dapagliflozin; Dulaglutide; Telmisartan; Urinary protein excretion rate; Inflammatory factor

糖尿病肾病(diabetic nephropathy)为糖尿病最严重、最常见的一种并发症,是导致终末期肾病的首要因素^[1-2]。徐华等^[3]研究显示,早期诊断糖尿病肾病能够有效减少终末期肾病的危险性。因此,早期治疗可有效阻止疾病进展,改善患者生活质量,提高存活率^[4]。替米沙坦为特异性血管紧张素 II 受体拮抗剂,也是临床治疗糖尿病肾病的一线药物,能够有效抑制肾小球硬化进程。达格列净能够抑制葡萄糖吸收,促进尿糖排泄,进而降低血糖水平;此外,还可降低血压、尿酸、尿蛋白等,保护肾脏^[5]。目前,联合用药一直为临床治疗糖尿病肾病常用方案^[6]。近期有学者研究提出,达格列净联合替米沙坦治疗糖尿病肾病虽然有效,但是效果一般,为了探讨更加有效的治疗方法,本研究在达格列净联合替米沙坦治疗的基础上,加用度拉糖肽治疗早期糖尿病肾病患者,并探究其对患者尿蛋白排泄率及血清炎症因子的影响,现报道如下。

1 资料与方法

1.1 临床资料 选取 2021 年 1—10 月山西省大同市第五人民医院内分泌科诊治早期糖尿病肾病患者 120 例,采用随机数字表法分为观察组和对照组,各 60 例。观察组男 42 例,女 18 例,年龄 35~68(45.23 ± 5.12)岁;体质指数 $22.78 \sim 25.13$ (23.57 ± 2.11) kg/m²;糖尿病病程 1~7(3.57 ± 1.02)年;基础疾病:高血压 12 例,高血脂 15 例;分期:Ⅰ期 32 例,Ⅱ期 28 例。对照组男 39 例,女 21 例,年龄 32~70(46.01 ± 5.21)岁;体质指数 $22.43 \sim 25.01$ (23.62 ± 2.17) kg/m²;糖尿病病程 1~8(3.62 ± 1.08)年;基础疾病:高血压 9 例,高血脂 16 例;分期:Ⅰ期 35 例,Ⅱ期 25 例。2 组性别、年龄、体质指数、糖尿病病程、基础疾病、分期等资料比较差异无统计学意义($P>0.05$),具有可比性。本研究经医院伦理委员会批准(2020-0926),患者及家属均知情同意并签署知情同意书。

1.2 病例选择标准 (1) 早期糖尿病肾病诊断标准^[7]:肾小球滤过率基本正常;持续性微量蛋白尿(尿

白蛋白与肌酐比值为 30~300 mg/g,3~6 个月内进行 3 次检测,至少有 2 次超过临界值)。(2) 纳入标准:①所有患者经血糖、尿蛋白排泄率等相关检查均符合“中国糖尿病肾脏疾病防治临床指南”^[7]诊断标准及“中国 2 型糖尿病防治指南”^[8]分型及诊断标准;②无精神疾病、家族遗传史或意识障碍患者。(3) 排除标准:①合并其他肾脏疾病患者;②近期发生过糖尿病急性并发症患者;③合并严重恶性肿瘤、恶性肿瘤及免疫系统、血液系统、肝脏系统疾病患者;④6 个月内有过脑血管病史、外伤及手术病史患者。

1.3 治疗方法 对照组患者入组后给予降糖药物、控制饮食、餐后运动等常规治疗,同时予达格列净片(阿斯利康制药有限公司生产)10 mg/次,每天 1 次口服,替米沙坦片(重庆莱美药业股份有限公司生产)40 mg/次,每天 1 次口服,若患者血压控制不理想,可将剂量增加至 80 mg/次,每天 1 次。观察组在对照组治疗基础上给予度拉糖肽(德国礼来制药有限公司)每周 1.5 mg 皮下注射。2 组均连续治疗 3 个月。

1.4 检测指标与方法

1.4.1 肾功能检测:于治疗前后抽取患者空腹肘静脉血 3 ml,分离血清,取上层清液,以酶法检测尿素氮(BUN)、尿酸(UA)水平,并计算肾小球滤过率(GFR)。于治疗前后留取患者 24 h 尿液,将其混匀后抽取 5 ml,以免疫比浊法检测尿蛋白水平,并计算尿蛋白排泄率。

1.4.2 血清炎症因子检测:上述血清以酶联免疫吸附法检测血清转化生长因子- β_1 (TGF- β_1)、白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平。

1.4.3 血糖水平检测:取上述血清以高压液相色谱法检测糖化血红蛋白(HbA_{1c})水平,以葡萄糖氧化酶法检测患者餐后 2 h 血糖(2 hPG)、空腹血糖(FPG)水平。

1.4.4 血脂水平检测:取上述血清,采用全自动生化分析仪(日本日立公司 7180 型),使用配套试剂,以酶联免疫吸附法检测患者血清总胆固醇(TC)、三酰甘油

(TG)、低密度脂蛋白胆固醇(LDL-C)及高密度脂蛋白胆固醇(HDL-C)水平。

1.4.5 不良反应发生率:记录并比较2组患者腹泻、腹痛、恶心呕吐、低血压、低血糖等不良反应的发生情况。

1.5 统计学方法 使用SPSS 22.0软件统计分析数据。正态分布的计量资料以 $\bar{x} \pm s$ 表示,组内及组间比较采用 t 检验;计数资料以频数或率(%)表示,组间比较采用 χ^2 检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 2组治疗前后肾功能指标比较 与治疗前比较,治疗后2组BUN、UA、尿蛋白排泄率水平均明显降低,GFR升高($P < 0.01$);与对照组比较,观察组BUN、UA、尿蛋白排泄率水平明显降低,GFR明显升高($P < 0.01$),见表1。

2.2 2组治疗前后血清炎症因子水平比较 与治疗前比较,2组治疗后血清TGF- β_1 、IL-6、TNF- α 水平均明显降低($P < 0.01$),且观察组低于对照组($P < 0.01$),见表2。

表2 对照组与观察组糖尿病肾病患者治疗前后血清炎症因子水平比较 ($\bar{x} \pm s$)

Tab. 2 Comparison of serum inflammatory factor levels between the control group and the observation group before and after treatment of diabetic nephropathy patients

组别	时间	TGF- β_1 ($\mu\text{g/L}$)	IL-6 (ng/L)	TNF- α (ng/L)
对照组 ($n=60$)	治疗前	150.42 $\pm$ 12.41	141.26 $\pm$ 10.64	31.76 $\pm$ 4.51
	治疗后	123.76 $\pm$ 9.11	126.78 $\pm$ 8.49	26.75 $\pm$ 3.14
观察组 ($n=60$)	治疗前	151.85 $\pm$ 12.57	142.57 $\pm$ 10.76	32.12 $\pm$ 4.56
	治疗后	105.64 $\pm$ 7.12	100.53 $\pm$ 7.12	19.23 $\pm$ 2.78
t/P 对照组内值		13.414 / <0.001	8.240 / <0.001	7.062 / <0.001
t/P 观察组内值		24.777 / <0.001	15.239 / <0.001	18.696 / <0.001
t/P 治疗后组间值		12.139 / <0.001	18.351 / <0.001	13.889 / <0.001

2.3 2组治疗前后血糖水平比较 与治疗前比较,治

疗后2组2 hPG、FPG、HbA_{1c}水平均明显降低($P < 0.01$),且观察组低于对照组($P < 0.01$),见表3。

表3 对照组与观察组糖尿病肾病患者治疗前后血糖水平比较 ($\bar{x} \pm s$)

Tab. 3 Comparison of blood glucose levels of diabetic nephropathy patients in the control group and the observation group before and after treatment

组别	时间	2 hPG (mmol/L)	FPG (mmol/L)	HbA _{1c} (%)
对照组 ($n=60$)	治疗前	14.68 $\pm$ 2.21	12.41 $\pm$ 1.92	8.53 $\pm$ 1.52
	治疗后	10.27 $\pm$ 1.57	8.53 $\pm$ 1.67	6.49 $\pm$ 1.24
观察组 ($n=60$)	治疗前	14.57 $\pm$ 2.14	12.62 $\pm$ 2.03	8.42 $\pm$ 1.46
	治疗后	8.51 $\pm$ 1.23	6.14 $\pm$ 1.26	5.37 $\pm$ 1.01
t/P 对照组内值		12.601 / <0.001	11.811 / <0.001	8.055 / <0.001
t/P 观察组内值		19.017 / <0.001	21.008 / <0.001	13.308 / <0.001
t/P 治疗后组间值		6.835 / <0.001	8.849 / <0.001	5.425 / <0.001

2.4 2组治疗前后血脂水平比较 与治疗前比较,治疗后2组患者血清TC、TG及LDL-C明显降低,观察组血清HDL-C水平明显升高($P < 0.01$),且观察组改善程度优于对照组($P < 0.01$),见表4。

2.5 2组不良反应发生率比较 治疗期间2组患者均无高血压、电解质紊乱及急性肾损伤情况发生。2组患者不良反应发生率比较差异无统计学意义($\chi^2 = 2.502$, $P = 0.114$),见表5。

3 讨论

糖尿病作为一种慢性疾病在临床较为常见,全球患病率可达7.2%~11.4%^[9]。随着病情进展,糖尿病可出现大血管及微血管并发症,如糖尿病肾病、神经病变、外周动脉病变、心血管病变及视网膜病变等,对患者生活质量可产生严重影响^[10]。Zhang等^[11]研究显示,我国糖尿病患者约10.8%合并慢性肾脏病,糖尿病肾病也是临床导致患者死亡的一项重要原因。因此,严格控制糖尿病患者血糖的同时还应积极保护患

表1 对照组与观察组糖尿病肾病患者治疗前后肾功能比较 ($\bar{x} \pm s$)

Tab. 1 Comparison of renal function of diabetic nephropathy patients in the control group and the observation group before and after treatment

组别	时间	BUN (mmol/L)	UA ($\mu\text{mol/L}$)	GFR (ml/min)	尿蛋白排泄率 (mg/g)
对照组 ($n=60$)	治疗前	6.61 $\pm$ 1.27	377.12 $\pm$ 20.41	83.11 $\pm$ 6.23	282.49 $\pm$ 19.76
	治疗后	5.42 $\pm$ 1.12	298.36 $\pm$ 16.21	108.42 $\pm$ 10.15	167.89 $\pm$ 16.23
观察组 ($n=60$)	治疗前	6.72 $\pm$ 1.35	378.42 $\pm$ 20.56	82.54 $\pm$ 6.12	281.56 $\pm$ 20.12
	治疗后	4.21 $\pm$ 1.01	241.58 $\pm$ 13.67	96.75 $\pm$ 9.71	143.52 $\pm$ 13.45
t/P 对照组内值		5.444 / <0.001	23.407 / <0.001	27.021 / <0.001	34.715 / <0.001
t/P 观察组内值		11.532 / <0.001	42.931 / <0.001	32.860 / <0.001	44.181 / <0.001
t/P 治疗后组间值		6.215 / <0.001	20.742 / <0.001	342.501 / <0.001	8.955 / <0.001

表 4 对照组与观察组糖尿病肾病患者治疗前后血脂水平比较 ($\bar{x} \pm s$, mmol/L)

Tab. 4 Comparison of blood lipid levels of diabetic nephropathy patients in the control group and the observation group before and after treatment

组别	时间	TC	TG	HDL-C	LDL-C
对照组 (n=60)	治疗前	6.98 ± 1.21	4.41 ± 0.52	0.96 ± 0.45	4.21 ± 0.79
	治疗后	5.24 ± 1.06	2.58 ± 0.47	1.05 ± 0.44	3.85 ± 0.71
观察组 (n=60)	治疗前	7.17 ± 1.04	4.33 ± 0.46	0.93 ± 0.42	4.25 ± 0.82
	治疗后	4.43 ± 1.04	1.14 ± 0.53	1.37 ± 0.41	3.33 ± 0.63
t/P 对照组内值		8.379 / <0.001	20.223 / <0.001	1.108 / 0.270	2.625 / 0.010
t/P 观察组内值		14.430 / <0.001	35.210 / <0.001	5.807 / <0.001	6.891 / <0.001
t/P 治疗后组间值		4.225 / <0.001	15.746 / <0.001	4.121 / <0.001	4.243 / <0.001

表 5 对照组与观察组糖尿病肾病患者不良反应发生率比较 [例(%)]

Tab. 5 Comparison of adverse reaction rate of diabetic nephropathy patients between the control group and the observation group

组别	例数	腹泻	上腹痛	恶心呕吐	低血压	低血糖	不良反应率(%)
对照组	60	1(1.67)	0	0	1(1.67)	1(1.67)	5.00
观察组	60	1(1.67)	1(1.67)	2(3.33)	2(3.33)	2(3.33)	13.33

者肾功能,以免导致肾功能恶化进而出现肾衰竭。

血管紧张素转化酶抑制剂可有效减少尿蛋白排泄,阻止早期糖尿病肾病进一步发展,目前已由中华医学会糖尿病分会及美国糖尿病学会推荐为首选药物^[5,12]。其中替米沙坦即为临床常用的血管紧张素转化酶抑制剂。达格列净为钠-葡萄糖协同转运蛋白 2 抑制剂,其降糖机制尤其适合用于血糖控制不佳糖尿病患者的联合用药,可减少其他降糖药剂量^[13]。任虎君等^[14]研究显示,达格列净不仅可有效控制血糖,还可保护患者肾脏功能,以防肾功能恶化,适用于糖尿病肾病患者。度拉糖肽是一种新型长效 GLP-1 受体激动剂的降糖药物,属于基因融合蛋白,近年来有学者研究认为^[15],此种药物不仅能够增加胰岛 β 细胞内环磷酸腺苷水平,且对改善胰岛素抵抗,促进胰岛素分泌,以及对改善胰岛的形态,调控胰岛细胞的增殖凋亡也具有一定的作用,另外对改善糖尿病患者肾脏功能也具有显著的效果,在达格列净联合替米沙坦治疗的基础上增加度拉糖肽可有效提高治疗效果。

本结果显示 2 组治疗后餐后 2 h 血糖、空腹血糖、糖化血红蛋白水平及 TC、TG、LDL-C、尿蛋白排泄率、BUN、UA 水平均明显降低,GFR 明显升高,且观察组改善效果优于对照组。与万磊^[16]研究结果一致。此结果说明,度拉糖肽联合达格列净、替米沙坦治疗早期糖尿病肾病可有效降低血糖、血脂及尿蛋白排泄率,改善肾功能。可能是因为替米沙坦可通过抑制血管紧张素 I 向血管紧张素 II 转换,进而减缓机体降解缓激肽,使循环系统血压降低,肾脏血流动力学得到改善,进而保护肾脏^[17];达格列净能够抑制肾脏近曲小管内钠-

葡萄糖协同转运蛋白 2 活性,进而降低上皮细胞对葡萄糖的重吸收,使尿糖排泄增加,进而达到降低血糖的目的。在此基础上增加 GLP-1 受体激动剂度拉糖肽共同作用于胰岛细胞,能够进一步起到改善胰岛素抵抗及肾功能的作用,降低血糖、血脂水平及尿蛋白排泄率,进一步提高临床疗效。

炎症反应在糖尿病肾病的发生、发展过程中起重要作用^[18-19]。其中 TGF-β₁、IL-6、TNF-α 为临床常见的促炎因子,多项研究显示 IL-6 与糖尿病微血管病变的发生关系密切;TNF-α 能够通过细胞凋亡、坏死及肾损伤产生肾脏细胞毒性作用,影响肾小球血液流变学,影响肾功能;TGF-β₁ 与多种炎症疾病的发生关系密切,其水平升高提示炎症反应的发生^[20]。本结果显示 2 组治疗后血清 TGF-β₁、IL-6、TNF-α 水平均明显降低,且观察组低于对照组。分析其原因,可能是因为达格列净联合替米沙坦可缓解糖尿病肾病的临床症状,减轻患者炎症反应,但是关于度拉糖肽对炎症反应的影响尚不明确。另外本研究还发现 2 组患者不良反应比较差异无统计学意义,这提示在达格列净联合替米沙坦治疗的基础上增加度拉糖肽不增加不良反应,且度拉糖肽自身还具有保护肝肾功能的作用,但容易引起低血糖或胃肠不适,因此临床应用中应针对患者具体的情况给予最佳的方案治疗。

综上所述,度拉糖肽联合达格列净治疗早期糖尿病肾病,可有效降低血清炎症因子水平及尿蛋白排泄率,减轻炎症反应,改善患者肾功能,调节血糖,阻止糖尿病肾病进一步发展,安全有效。但是本研究纳入样本量相对较少,可能会导致研究结果出现偏倚,还需在

以后研究中扩大样本量验证本研究结果。

利益冲突: 所有作者声明无利益冲突

作者贡献声明

邢建东、姚艳琴、李银玉: 设计研究方案, 实施研究过程, 论文撰写; 马春明: 提出研究思路, 分析试验数据, 论文审核; 陈海丽: 实施研究过程, 资料搜集整理, 论文修改; 王静如: 进行统计学分析

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