·临床研究·

达格列净治疗早期糖尿病肾病的疗效以及对调节性T细胞的影响

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[摘 要] **目的**:观察达格列净对早期糖尿病肾病(diabetic kidney disease,DKD)患者的疗效及对调节性T细胞(regulatory T cell,Treg)和炎症因子的影响。**方法**:入选2019年8—12月南京医科大学附属江宁医院门诊收治的DKD患者47例为研究对象。所有患者在原先降糖治疗的基础上均给予达格列净10 mg/d,口服4周,保持饮食以及运动方式不变。比较治疗前后静脉空腹血糖(fasting blood glucose,FBG)、糖化白蛋白(glycated albumin,GA)、尿白蛋白-肌酐比值(urinary albumin/creatinine ratio,UACR)、24 h尿蛋白定量、估算的肾小球滤过率(estimated glomerular filtration rate,eGFR)、外周血Treg、外周血白介素(interleukin,IL)-6、IL-1β、肿瘤坏死因子(tumor necrosis factor,TNF)-β和IL-10的水平,并记录药物不良反应。**结果**:达格列净治疗4周后 FBG[(8.96±0.83)mmol/L *vs.* (7.42 ± 0.67)mmol/L]、GA[(18.47 ± 3.32)% *vs.* (15.49 ± 2.62)%]、24 h 尿蛋白定量[1.14(0.29,2.08)g/24 h *vs.* 0.28(0.15,0.83)g/24 h]以及UACR[80(45,150)mg/g *vs.* 40(30,80)mg/g]较治疗前均明显下降($P < 0.05$),eGFR较治疗前也有所下降[(105.30 ± 36.01)mL/(min·1.73 m^2) *vs.* (92.07 ± 35.26)mL/(min·1.73 m^2),$P < 0.05$],但在治疗8周后可恢复至治疗前水平[(104.88 ± 36.86)mL/(min·1.73 m^2) *vs.* (105.30 ± 36.01)mL/(min·1.73 m^2),$P > 0.05$]。治疗4周后Treg的表达量较治疗前明显上调[(3.19 ± 0.74)% *vs.* (5.64 ± 0.93)%,$P < 0.05$],促炎因子IL-1β[(7.83 ± 1.39)ng/L *vs.* (4.57 ± 0.71)ng/L]、TNF-β[(372.85 ± 6.79)ng/L *vs.* (227.62 ± 7.29)ng/L]、IL-6[(3.99 ± 0.47)ng/L *vs.* (2.59 ± 1.01)ng/L]的表达量较治疗前明显下调($P < 0.05$),抑炎因子IL-10的表达量较治疗前上调[(0.03 ± 0.01)ng/mL *vs.* (0.05 ± 0.01)ng/mL,$P < 0.05$]。治疗期间,无患者出现低血糖、酮症等不良反应,有5例患者出现无症状性尿路感染。**结论**:达格列净可能通过上调Treg的表达来抑制炎症反应,对DKD具有肾脏保护作用。

[关键词] 达格列净;糖尿病肾病;调节性T细胞;炎症反应

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The efficacy of dapagliflozin on patients with early diabetic kidney disease and the influence on the expression of regulatory T cells

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[**Abstract**] **Objective**: This study aims to observe the efficacy of dapagliflozin on patients with early diabetic kidney disease (DKD) and the influence on expression of regulatory T cells (Tregs) and inflammatory factors. **Methods**: Forty-seven patients who developed DKD between August 2019 and December 2019 in the Affiliated Jiangning Hospital of Nanjing Medical University were enrolled. On the basis of the original hypoglycemic therapy, all patients were prescribed dapagliflozin 10 mg, qd, orally, for 4 weeks and kept diet and exercise mode unchanged. Fasting plasma glucose (FBG), glycated albumin (GA), urinary albumin creatinine ratio (UACR), 24-hour urinary protein and estimated glomerular filtration rate (eGFR) were compared between baseline and 4-week after prescription. The level of Tregs in peripheral blood detected by flow cytometry, the levels of interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-β and IL-10 measured by ELISA were also compared. Adverse drug reactions were recorded. **Results**: After 4 weeks of dapagliflozin treatment,

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FBG[(8.96 ± 0.83 mmol/L)*vs*. (7.42 ± 0.67)mmol/L], GA[(18.47 ± 3.32)% *vs*. (15.49 ± 2.62)%], 24 h urine protein quantification [1.14(0.29, 2.08)g/24 h *vs*. 0.28(0.15, 0.83)g/24 h], UACR[80(45, 150)mg/g *vs*. 40(30, 80)mg/g] and eGFR[(105.30 ± 36.01) mL/(min·1.73 m^2)*vs*. (92.07 ± 35.26)mL/(min·1.73 m^2)] were significantly lower than baseline($P < 0.05$). However, after 8 weeks of treatment, the eGFR could return to the level before treatment [(104.88 ± 36.86) mL/(min·1.73 m^2) *vs*. (105.30 ± 36.01) mL/(min·1.73 m^2), $P > 0.05$]. Compared with baseline, the expression of Tregs was significantly up-regulated[(3.19 ± 0.74)% *vs*. (5.64 ± 0.93)%, $P < 0.05$], the pro-inflammatory factors IL-1β[(7.83 ± 1.39)ng/L *vs*. (4.57 ± 0.71)ng/L], TNF-β[(372.85 ± 6.79) ng/L *vs*. (227.62 ± 7.29)ng/L], IL-6[(3.99 ± 0.47)ng/L *vs*. (2.59 ± 1.01)ng/L] was significantly down-regulated($P < 0.05$), and the expression of the anti-inflammatory factor IL-10 was up-regulated[(0.03 ± 0.01)ng/mL *vs*. (0.05 ± 0.01)ng/mL, $P < 0.05$]. There were no adverse reactions such as hypoglycemia and ketosis, and 5 patients had asymptomatic urinary tract infection during the treatment period. **Conclusion**: Dapagliflozin may up-regulate the expression of Tregs to inhibit the inflammatory response and ultimately play a role in renal protection in DKD patients.

[**Key words**] dapagliflozin; diabetic kidney disease; Treg; inflammatory response

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糖尿病肾病(diabetic kidney disease, DKD)是2型糖尿病(type 2 diabetes mellitus, T2DM)的主要并发症,是慢性肾脏病(chronic kidney disease, CKD)的主要病因,主要临床表现为尿白蛋白增高和/或肾小球滤过率下降[1]。随着科学技术的发展,近年来对DKD损伤致病因素的认识逐渐从代谢和血流动力学异常的宏观层面转向基因和分子层面,其中最重要的转变是免疫炎症被认为与DKD的发病机制密切相关。调节性T细胞(regulatory T cell, Treg)是1995年由Sakaguchi报道的以$CD4^+CD25^+$为特征的T细胞[2],进一步研究证实$Foxp3^+$是调控调节性T细胞发育和功能的关键转录因子[3]。研究表明,Treg可以通过多种机制下调促炎因子,如白介素(interleukin, IL)-6、IL-1β、肿瘤坏死因子(tumor necrosis factor, TNF)-β等,上调抑炎因子如IL-10,在维持免疫稳态中起着至关重要的作用[4-6]。达格列净是钠-葡萄糖协同转运蛋白2(sodium-glucose cotransporter-2, SGLT2)抑制剂,该药可选择性阻断SGLT2,减少近曲小管对葡萄糖的重吸收,增加葡萄糖在尿液中的排泄,从而降低血糖。越多越多的研究也表明,达格列净除了降糖外,还可以降压、降低DKD患者尿蛋白,最终发挥保护肾脏的作用[7-9]。本文通过观察达格列净治疗早期DKD患者的疗效及对Treg、促炎因子IL-6、IL-1β、TNF-β和抑炎因子IL-10的影响,探讨DKD与Treg的关系以及达格列净可能的治疗机制。

1　对象和方法

1.1　对象

采用单中心、前瞻性、自身前后对照临床研究方法,根据纳入标准入选2019年8月1日—12月31日在本院门诊收治的DKD患者47例为研究对象,根据排除标准排除了6例患者。所有研究对象均在入组前签署知情同意书并经过本院伦理委员会批准(伦理批件号:2019-03-019-K01)。所有患者在原先降糖治疗的基础上均给予达格列净10 mg,每天1次,口服4周,保持饮食以及运动方式不变。

纳入标准:符合1990年世界卫生组织关于T2DM的诊断,同时符合2019年中国糖尿病肾脏疾病防治临床指南中DKD的诊断[1]:20~80岁血糖控制不佳[糖化血红蛋白(glycated hemoglobin A1c, HbA1c)7.0%~10.0%],尿白蛋白-肌酐比值(urinary albumin/creatinine ratio, UACR)≥30 mg/g,估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)≥45 mL/(min·1.73 m^2)(定义为早期DKD)。正在服用血管紧张素转换酶抑制剂或血管紧张素受体阻断剂类药物且剂量稳定2个月。

排除标准:怀孕或哺乳的妇女;肝功能严重异常;急性充血性心力衰竭;入组前6个月内有糖尿病酮症酸中毒、糖尿病昏迷病史;严重感染;手术前或手术后;严重创伤;已知对达格列净过敏;入组前1个月持续使用SGLT2抑制剂治疗或有SGLT2抑制剂治疗史。

1.2　方法

1.2.1　一般检测

治疗前收集患者一般资料,包括年龄、性别、T2DM病程、体重指数(body mass index, BMI)、用药情况、合并症等。治疗前后采集静脉血检测患者静脉空腹血糖(fasting blood glucose, FBG)、糖化白蛋白

(glycated albumin,GA)、HbA1c、尿常规、肝肾功能、电解质,检测24 h尿蛋白定量、UACR,利用MDRD公式计算eGFR[$eGFR_{MDRD}=186\times Scr^{-1.154}\times Age^{-0.203}$(×0.742如果为女性),Scr:血肌酐(mg/dL),Age:年龄(岁)][10],记录不良反应。

1.2.2 Treg检测

治疗前后采集患者静脉血,利用流式细胞学技术检测Treg的表达量,具体步骤如下:①CD4、CD25的抗体各取3 μL加入50 μL全血中,2~8℃避光孵育30 min;②400 *g*离心5 min,弃去上清液,加入Flow cytometry staining buffer清洗细胞,离心,弃上清;③加500 μL固定剂,室温下避光孵育50 min;④不需要清洗,加入1 mL破膜剂,室温下以400 *g*离心5 min,弃上清;⑤将细胞重悬于100 μL Flow cytometry staining buffer,加入稀释好的Foxp3抗体2 μL,4 ℃避光过夜后上机检测。所有样品均在BD Accuri C6 Plus流式细胞仪上进行分析。使用BD CSampler™ Plus软件进行分析。检测外周血Treg的eBioscience™ Human Regulatory T Cell Staining Kit购自美国Ebioscience公司。

1.2.3 炎症因子的检测

IL-1β、IL-6、IL-10以及TNF-β均采用ELISA方法检测,按照试剂盒说明书进行操作。所有试剂盒均购自美国Ebioscience公司。

1.3 统计学方法

采用SPSS25.0统计软件进行数据的统计分析,计量资料采用均数±标准差($\bar{x}\pm s$)表示,不符合正态分布的计量资料以中位数(四分位数)[$M(P_{25},P_{75})$]表示,自身前后对照采用配对*t*检验或Wilcoxon符号秩检验;计数资料采用频率或百分比表示。$P<0.05$为差异有统计学意义。

2 结 果

2.1 一般情况

本研究共纳入患者47例,患者一般资料见表1。

2.2 临床疗效评估

达格列净治疗4周后FBG[(8.96 ± 0.83)mmol/L *vs.* (7.42 ± 0.67)mmol/L]、GA[(18.47 ± 3.32)% *vs.* (15.49 ± 2.62)%]、24 h尿蛋白定量[1.14(0.29,2.08)g/24 h *vs.* 0.28(0.15,0.83)g/24 h]以及UACR[80(45,150)mg/g *vs.* 40(30,80)mg/g]较治疗前均明显下降,差异有统计学意义($P<0.05$),治疗4周后eGFR较治疗前亦有所下降[(105.30 ± 36.01)mL/(min·1.73 m²) *vs.* (92.07 ± 35.26)mL/(min·1.73 m²),$P<0.05$],治疗8周后eGFR可恢复至治疗前水平[(104.88 ± 36.86)mL/(min·1.73 m²) *vs.* (105.30 ± 36.01)mL/(min·1.73 m²),$P>0.05$,表2]。

表1 47例早期DKD患者的一般资料

Table 1 General information of 47 patients with early DKD

项目	数值(n=47)
性别(男/女,*n*/*n*)	37/10
年龄(岁,$\bar{x}\pm s$)	55 ± 12
病程[年,$M(P_{25},P_{75})$]	9(4,14)
BMI(kg/m²,$\bar{x}\pm s$)	27.74 ± 4.16
合并糖尿病视网膜病变[*n*(%)]	18(38.30)
合并高血压[*n*(%)]	39(82.98)
单纯饮食+运动降糖[*n*(%)]	6(12.77)
胰岛素降糖[*n*(%)]	11(23.40)
胰岛素+口服降糖药[*n*(%)]	17(36.17)
口服降糖药降糖[*n*(%)]	13(27.66)
FBG(mmol/L,$\bar{x}\pm s$)	8.96 ± 0.83
HbA1c(%,$\bar{x}\pm s$)	8.42 ± 1.37
GA(%,$\bar{x}\pm s$)	18.47 ± 3.32
24 h尿蛋白定量[g/24 h,$M(P_{25},P_{75})$]	1.14(0.29,2.08)
UACR[mg/g,$M(P_{25},P_{75})$]	80(45,150)
血尿素氮(mmol/L,$\bar{x}\pm s$)	6.84 ± 2.15
血肌酐(μmol/L,$\bar{x}\pm s$)	75.64 ± 26.34
eGFR[mL/(min·1.73 m²),$\bar{x}\pm s$]	105.30 ± 36.01

2.3 Treg比较

达格列净治疗4周后,与治疗前相比T细胞的标志物$CD4^+$的阳性率显著升高,同时$CD25^+Foxp3^+$的阳性率也显著升高,结果显示达格列净可显著上调Treg的表达量[(3.19 ± 0.74)% *vs.* (5.64 ± 0.93)%,$P<0.05$,图1、表3]。

表2 治疗前后FBG、GA、24 h尿蛋白、UACR、eGFR指标比较

Table 2 Comparison of FBG, GA, 24 h urine protein quantification, UACR, eGFR before and after treatment

时间	FBG(mmol/L)	GA(%)	24 h尿蛋白定量(g/24 h)	UACR(mg/g)	eGFR[mL/(min·1.73 m²)]
治疗前	8.96 ± 0.83	18.47 ± 3.32	1.14(0.29,2.08)	80(45,150)	105.30 ± 36.01
治疗4周后	7.42 ± 0.67*	15.49 ± 2.62*	0.28(0.15,0.83)*	40(30,80)*	92.07 ± 35.26*
治疗8周后	—	—	—	—	104.88 ± 36.86**

与治疗前相比,*$P<0.05$;与治疗4周后比,**$P<0.05$,n=47。

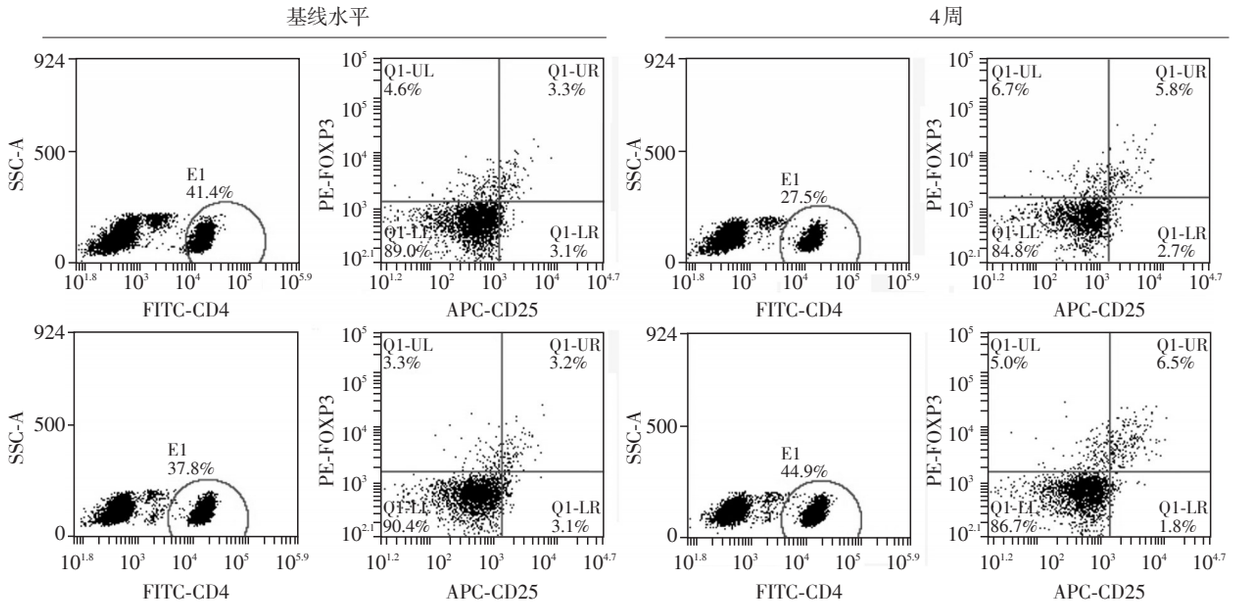

图1　流式细胞术检测DKD患者静脉血$CD4^+CD25^+Foxp3^+$Treg含量的变化

Figure 1　Changes of $CD4^+CD25^+Foxp3^+$Tregs in venous blood of DKD patients detected by flow cytometry

2.4　炎症因子比较

达格列净治疗4周后促炎因子IL-1β[(7.83 ± 1.39)ng/L *vs.* (4.57 ± 0.71)ng/L]、TNF-β[(372.85 ± 6.79)ng/L *vs.* (227.62 ± 7.29)ng/L]、IL-6[(3.99 ± 0.47)ng/L *vs.* (2.59 ± 1.01)ng/L]的表达量明显下调，差异有统计学意义($P < 0.05$)，且抑炎因子IL-10的表达量较治疗前上调[(0.03 ± 0.01)ng/mL *vs.* (0.05 ± 0.01)ng/mL，$P < 0.05$，表3]。

表3　治疗前后Treg和炎症指标比较

Table 3　Comparison of Tregs and inflammatory factors before and after treatment　($\bar{x} \pm s$)

时间	Treg(%)	IL-1β(ng/L)	TNF-β(ng/L)	IL-6(ng/L)	IL-10(ng/mL)
治疗前	3.19 ± 0.74	7.83 ± 1.39	372.85 ± 6.79	3.99 ± 0.47	0.03 ± 0.01
治疗4周后	5.64 ± 0.93*	4.57 ± 0.71*	227.62 ± 7.29*	2.59 ± 1.01*	0.05 ± 0.01*

与治疗前相比，*$P < 0.05$，n=47。

2.5　安全性

治疗期间，无患者出现低血糖、酮症等不良反应，有5例患者出现无症状性尿路感染，考虑患者无明显尿路刺激症状，嘱患者多饮水、勤排尿、避免憋尿，8周后复查尿常规均正常。

3　讨　论

近年来，T2DM的发病率逐年升高，且我国糖尿病人群尿毒症患病风险远远高于国外人群[1]。DKD是T2DM引起的糖尿病微血管并发症，被视为T2DM特有的、与血糖控制水平密切相关的并发症之一。蛋白尿是T2DM患者DKD恶化和心血管疾病(cardiovascular diseases，CVD)发病的重要危险因素[11-12]。DKD的发病机制主要包括血流动力学异常、细胞内代谢异常、晚期糖基化终产物的形成，越来越多的研究表明炎症状态以及氧化应激也参与了DKD的病理过程中[13-14]。

肾小管近曲小管细胞刷状缘主要存在两种不同功能的载体，SGLT1和SGLT2。SGLT1主要分布在小肠、肾脏、心脏和脑，其主要生理功能是在小肠完成对葡萄糖的吸收。SGLT2特异性地分布在肾脏近曲小管S1部位，负责约90%葡萄糖的重吸收。达格列净作为新型降糖药，通过阻断肾脏的SGLT2，发挥降糖、降压等作用。本文通过前瞻性、自身对照研究发现，口服达格列净4周后，可以明显降低患者FBG、GA、24 h尿蛋白定量以及UACR，这与大多数的研究结果一致[15-17]。需要指出的是由于24 h尿蛋白留取的复杂性，因此大多数研究均采用UACR来评估达格列净的降尿蛋白作用，本文除了采用UACR，还采用24 h尿蛋白定量评估蛋白尿情况，因此结果具有较强的说服力以及准确性。在口服达格列净4周后，患者的eGFR下降。Neuen等[18]也发

现,在口服达格列净治疗的早期,会出现eGFR的下降,但是这种肾功能的下降会在1周左右消失。这种eGFR可逆性的改变表明早期eGFR的变化并不是因为肾脏损伤引起的,而是由于血流动力学改变引起的肾脏血流量减少[19]。达格列净通过特异性阻断SGLT2,增加了钠向致密斑的输送,最终引起入球小动脉收缩,肾小球内压降低,单个肾单位可逆性下降。为了证实这种猜想,我们继续随访了4周,在达格列净治疗8周后,发现降低的eGFR可恢复至治疗前水平。也有研究指出,肾小球内压的降低与肾脏的保护作用密切相关[20]。

DKD的发生发展与炎症密切相关,研究表明达格列净通过抑制葡萄糖进入肾脏发挥抗炎作用,最终发挥降低尿蛋白作用[21]。Elkazzaz等[22]通过小鼠实验发现达格列净可以降低DKD小鼠体内的炎症因子从而降低尿蛋白,发挥保护肾脏的作用。Treg可以通过多种机制抑制促炎因子的产生而促进抑炎因子的产生[6,23]。Treg对于肾脏的保护作用已经在多个肾脏模型中得到了证实,如肾移植模型[24]、缺血再灌注损伤模型[25]等。进一步研究表明,Treg可以通过多种机制如抑制效应T细胞以及分泌多种抗炎症因子等起到调节局部免疫以及炎症反应的作用,进而发挥对损伤脏器的保护作用。我们在前期研究中发现Treg可以改善梗阻性肾病的肾脏纤维化[26],因此为了进一步研究达格列净降低尿蛋白的具体机制,本研究利用流式细胞学技术检测了患者血清中Treg的表达量以及相关炎症因子,结果显示达格列净治疗4周后,与用药前相比血清中$CD25^+$ $Foxp3^+$的阳性率升高,$Foxp3^+$作为Treg谱系的主要转录因子,其阳性率升高提示Treg表达的上调。与此同时,促炎因子IL-6、IL-1β、TNF-β的表达量明显降低,而抑炎因子IL-10的表达量明显增加。本研究表明达格列净有可能通过上调Treg的含量来调控炎症反应,最终发挥降低尿蛋白以及肾脏保护的作用。前期临床研究显示,DKD的发病过程中伴随辅助性T细胞17(T helper 17,Th17)和Treg亚群之间的失衡[27-28],其中Th17极化主要由血清/糖皮质激素调节激酶1(serum/glucocorticoid-regulated kinase 1,SGK1)介导。2021年Wang等[29]通过小鼠实验发现,达格列净通过下调SGK1的表达来逆转Th17和Treg的失衡,最终发挥肾脏保护作用。此外,SGLT2抑制剂通过调节肾小管中钠的转运,可间接参与调节Treg的活性[21,30],但具体机制仍需要更多研究来阐述。

本文通过单中心、前瞻性、自身对照研究表明达格列净降糖效果显著,并且可以降低尿蛋白发挥肾脏保护作用,在口服达格列净治疗早期会出现eGFR一过性的下降,但这种下降具有可逆性。另外,达格列净可以上调Treg的含量,抑制炎症反应。但是本文也有一些不足,首先,本文为单中心研究,样本量较小,因此结论具有一定局限性;此外关于达格列净如何上调Treg、抑制炎症反应,本文并未进行具体研究。因此,在下一步研究中,将通过动物实验进一步阐述达格列净通过调节Treg发挥肾脏保护作用的具体机制。

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