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# 达格列净联合二甲双胍治疗 2 型糖尿病的疗效及对糖脂代谢的影响 \*

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**摘要 目的:**探讨达格列净联合二甲双胍治疗 2 型糖尿病的疗效及对糖脂代谢的影响。**方法:**选择 2018 年 1 月-2020 年 1 月在我院接受治疗的 120 例 2 型糖尿病患者,采用抽签法分为观察组(n=61)和对照组(n=59)。对照组给予二甲双胍治疗,观察组在对照组的基础上给予达格列净治疗。比较两组患者的临床疗效、治疗前后血清空腹血糖 (FBG)、空腹胰岛素 (FINS)、糖化血红蛋白 (HbA1c)、总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)水平、胰岛素 $\beta$  细胞功能指数(HOMA- $\beta$ )、胰岛素抵抗指数(HOMA-IR)的变化情况及不良反应的发生情况。**结果:**治疗后,观察组和对照组总有效率分别为 93.62%, 74.47%, 观察组显著高于对照组( $P<0.05$ ); 两组 FBG、FINS、HbA1c、TC、TG、LDL-C 水平及 HOMA-IR 均较治疗前显著降低,且观察组上述指标均明显低于对照组( $P<0.05$ ), 两组 HDL-C 水平和 HOMA- $\beta$  均较治疗前显著升高,且观察组显著高于对照组( $P<0.05$ ); 两组不良反应总发生率为 6.56%、8.47%, 组间比较差异无统计学意义( $P>0.05$ )。**结论:**达格列净联合二甲双胍治疗 2 型糖尿病的效果显著优于单用二甲双胍治疗,其可有效改善患者糖脂代谢水平,且不会增加不良反应。

**关键词:**达格列净;二甲双胍;2 型糖尿病;糖脂代谢

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## Efficacy of Dagulijing Combined with Metformin in the Treatment of Type 2 Diabetes Mellitus and Its Effect on the Glucose and Lipid Metabolism\*

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**ABSTRACT Objective:** To study the efficacy of dagulijing combined with metformin in the treatment of type 2 diabetes mellitus and its effect on glucose and lipid metabolism. **Methods:** 120 patients with type 2 diabetes who were treated in our hospital from January 2018 to January 2020 were selected and divided into the observation group (n=61) and the control group (n=59) by drawing lots. The control group was treated with metformin, and the observation group was treated with daguernet on the basis of control group. The clinical efficacy, changes of serum fasting blood glucose (FBG), fasting insulin (FINS), glycosylated hemoglobin (HbA1c), total cholesterol (TC), three acyl glycerin (TG), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) levels and insulin beta cell function index (HOMA-beta), insulin resistance index (HOMA IR) before and after treatment and the occurrence of adverse reactions were compared between two groups. **Results:** After treatment, the total effective rate was 93.62% in the observation group and 74.47% in the control group, which was significantly higher in the observation group than that in the control group ( $P<0.05$ ). The levels of FBG, FINS, HbA1c, TC, TG, ldl-c and HOMA-IR in the two groups were significantly lower than those in the control group before treatment, and the above indexes in the observation group were significantly lower than those in the control group ( $P<0.05$ ). The total incidence of adverse reactions between the two groups was 6.56% and 8.47%, no significant difference was found between the two groups ( $P>0.05$ ). **Conclusion:** The effect of dagulijing combined with metformin in the treatment of type 2 diabetes was significantly better than that of metformin alone, which could effectively improve the glucose and lipid metabolism of patients without increasing adverse reactions.

**Key words:** Daglitzim; Metformin; Type 2 diabetes; Glucose and lipid metabolism

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## 前言

糖尿病是一组以高血糖为特征的代谢性疾病,根据胰岛素功能状况分为 1 型糖尿病和 2 型糖尿病,其中约 90% 患者为 2 型糖尿病,该病可发生于任何年龄,起病较为隐匿,无明显症状<sup>[1,2]</sup>。近年来,2 型糖尿病的发病率呈逐年上升趋势,我国以 1.14 亿糖尿病患者位居世界糖尿病首位,到 2045 年预计增长至 1.2 亿人<sup>[12]</sup>。因此,对 2 型糖尿病患者给予及时有效治疗在临床中具有重要意义。

胰岛素抵抗被认为是 2 型糖尿病发病的主要原因,糖脂代谢异常为胰岛素抵抗的表征<sup>[3]</sup>。二甲双胍是临床治疗糖尿病的常用药物,可强化胰岛素敏感性,提高非胰岛素依赖的组织对葡萄糖的利用,但目前临床上单一药物已不能获得较好的降糖效果<sup>[4,5]</sup>。达格列净属于钠-葡萄糖协同转运蛋白 2 抑制剂,是一种新型口服降糖药,能通过抑制钠-葡萄糖协同转运蛋白而减少肾小管重吸收滤过葡萄糖,促进葡萄糖的排泄,进而发挥降低血糖的作用<sup>[6-8]</sup>。基于此,本研究主要探讨了达格列净联合二甲双胍治疗 2 型糖尿病的疗效及其对糖脂代谢的影响,现报道如下。

## 1 资料与方法

### 1.1 一般资料

选择 2018 年 1 月-2020 年 1 月在我院接受治疗的 120 例 2 型糖尿病患者。采用抽签法分为 2 组。观察组 61 例:男 33 例,女 28 例,年龄 47-75 岁,平均(61.25±4.21)岁,病程 2~10 年,平均(6.53±1.24)年,平均体质量指数(27.56±2.35)kg/m<sup>2</sup>;对照组 59 例,男 31 例,女 28 例,年龄 45-74 岁,平均(61.23±4.18)岁,病程 2~9 年,平均(6.48±1.23)年,平均体质量指数(27.62±2.32)kg/m<sup>2</sup>。两组基线资料比较无明显差异( $P>0.05$ ),具有可比性。

2 型糖尿病的诊断参照《中国 2 型糖尿病防治指南》<sup>[9]</sup>,(1)FBG≥7 mmol/L;(2)烦渴多饮、多尿、多食;(3)餐后 2 h 血糖≥

11.1 mmol/L。纳入标准:(1)符合上述诊断标准;(2)临床资料完整;(3)血流动力学稳定;(4)无其他严重疾病;(5)无胰岛素治疗史;(6)签署知情同意书。排除标准:(1)重症有生命危险患者;(2)患有意识障碍、精神障碍者;(3)心功能异常者;(4)合并严重心律失常患者;(5)急性感染者;(6)血液系统异常者;(7)依从性较差者;(8)对本次研究药物过敏者。

### 1.2 治疗方法

两组均给予饮食管理、运动干预等常规治疗。对照组给予二甲双胍(规格:500mg,生产厂家:Boehringer Ingelheim Pharma GmbH & Co. KG, 国药准字:H20190024)0.5 g 口服治疗,1d3 次。观察组在对照组的基础上加用达格列净(规格:5mg;生产厂家:AstraZeneca Pharmaceuticals LP; 国药准字 H20170205)10 mg/次,早餐前口服,1d1 次。

### 1.3 观察指标

采集空腹静脉血 5mL,以 3000r·min<sup>-1</sup> 的速度进行离心,时间 10 min,提取上层血清后,置于零下 20℃ 的冷冻箱内存储以备检测,采用双抗体夹心酶联免疫吸附法测定 TC、TG、LDL-C、HDL-C 水平;采用全自动分析仪检测 FBG、FINS、HbA1c 水平;记录不良反应的发生情况。

疗效评定标准:显效:血糖、血压各项恢复正常,症状消失;有效:症状消失,血红蛋白小于 6.2%;无效:无明显改善或加重。

### 1.4 统计学分析

以 SPSS18.0 软件包处理实验数据,符合正态分布计量资料用均数±标准差( $\bar{x} \pm s$ )表示,组间比较使用独立样本 t 检验,计数资料以率表示,组间比较采用  $\chi^2$  检验,以  $P<0.05$  表示差异具有统计学意义。

## 2 结果

### 2.1 两组疗效的比较

治疗后,观察组和对照组总有效率分别为 93.62%,74.47%,观察组显著高于对照组( $P<0.05$ ),见表 1。

表 1 两组疗效的比较[例(%)]

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

| Groups            | n  | Excellent | Valid     | Invalid   | Total effective rate |
|-------------------|----|-----------|-----------|-----------|----------------------|
| Observation group | 61 | 29(47.54) | 18(29.51) | 14(22.95) | 47(77.05)            |
| Control group     | 59 | 15(25.42) | 19(32.20) | 25(42.37) | 34(57.63)            |
| $\chi^2$ value    |    |           |           |           | 5.157                |
| $P$ value         |    |           |           |           | 0.023                |

### 2.2 两组治疗前后血糖水平的比较

治疗前,两组血糖水平比较差异无明显统计学意义( $P>0.05$ );治疗后,两组 FBG、FINS、HbA1c 水平均较治疗前显著降低( $P<0.05$ ),且观察组上述指标均低于对照组( $P<0.05$ ),见表 2。

### 2.3 两组治疗前后血脂水平的比较

治疗前,两组血脂水平比较差异无明显统计学意义( $P>0.05$ );治疗后,两组 TC、TG、LDL-C 水平均较治疗前显著降低( $P<0.05$ ),且观察组明显低于对照组( $P<0.05$ ),两组 HDL-C 水平较治疗前显著升高( $P<0.05$ ),且观察组明显高于对照组( $P<0.05$ ),见表 3。

### 2.4 两组治疗前后胰岛素功能的比较

治疗前,两组 HOMA- $\beta$ 、HOMA-IR 比较差异无明显统计学意义( $P>0.05$ );治疗后,两组 HOMA- $\beta$  水平均较治疗前显著升高( $P<0.05$ ),且观察组高于对照组( $P<0.05$ ),两组 HOMA-IR 水平较治疗前显著降低( $P<0.05$ ),且观察组低于对照组( $P<0.05$ ),见表 4。

### 2.5 两组不良反应发生情况的比较

两组不良反应总发生率为 6.56%、8.47%,组间比较差异无统计学意义( $P>0.05$ ),见表 5。

表 2 两组治疗前后血糖水平的比较( $\bar{x} \pm s$ )Table 2 Comparison of the blood glucose levels between the two groups before and after treatment( $\bar{x} \pm s$ )

| Groups            | n  | FBG(mmol/L)      |                 | FINS(mmol/L)     |                 | HbA1c(%)         |                 |
|-------------------|----|------------------|-----------------|------------------|-----------------|------------------|-----------------|
|                   |    | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 61 | 9.45± 2.71       | 6.14± 0.41      | 9.68± 1.61       | 6.11± 0.42      | 8.87± 1.57       | 7.12± 0.16      |
| Control group     | 59 | 9.51± 2.69       | 6.98± 0.24      | 9.65± 1.59       | 7.35± 0.69      | 8.91± 1.73       | 7.98± 0.21      |
| t value           |    | 0.122            | 13.637          | 0.103            | 11.936          | 0.133            | 25.286          |
| P value           |    | 0.903            | 0.000           | 0.918            | 0.000           | 0.895            | 0.000           |

表 3 两组治疗前后血脂水平比较( $\bar{x} \pm s$ , mmol/L)Table 3 Comparison of the blood lipid levels between the two groups before and after treatment( $\bar{x} \pm s$ , mmol/L)

| Groups            | n  | TC               |                 | TG               |                 | LDL-C            |                 | HDL-C            |                 |
|-------------------|----|------------------|-----------------|------------------|-----------------|------------------|-----------------|------------------|-----------------|
|                   |    | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Observation group | 61 | 8.71± 1.17       | 6.04± 1.02      | 6.59± 0.89       | 4.61± 0.61      | 5.15± 0.41       | 2.23± 0.41      | 1.23± 0.29       | 1.69± 0.61      |
| Control group     | 59 | 8.68± 1.19       | 6.56± 1.14      | 6.63± 0.87       | 5.25± 0.58      | 5.19± 0.37       | 3.29± 0.47      | 1.25± 0.32       | 1.47± 0.51      |
| t value           |    | 0.139            | 2.635           | 0.249            | 5.886           | 0.560            | 13.178          | 0.359            | 2.139           |
| P value           |    | 0.889            | 0.009           | 0.804            | 0.000           | 0.576            | 0.000           | 0.720            | 0.034           |

表 4 两组治疗前后胰岛素功能比较( $\bar{x} \pm s$ )Table 4 Comparison of insulin function between the two groups before and after treatment( $\bar{x} \pm s$ )

| Groups            | n  | HOMA-β               |                 | HOMA-IR              |                 |
|-------------------|----|----------------------|-----------------|----------------------|-----------------|
|                   |    | Before the treatment | After treatment | Before the treatment | After treatment |
| Observation group | 61 | 6.24± 0.87           | 10.36± 1.51     | 3.52± 0.54           | 2.01± 0.21      |
| Control group     | 59 | 6.27± 0.85           | 8.45± 1.24      | 3.49± 0.52           | 3.06± 0.34      |
| t value           |    | 0.191                | 7.558           | 0.309                | 20.427          |
| P value           |    | 0.849                | 0.000           | 0.757                | 0.000           |

表 5 两组不良反应发生情况的比较[例(%)]

Table 5 Comparison of the incidence of adverse reactions between the two groups[n(%)]

| Groups            | n  | Nausea | Vomiting | Diarrhea | The total incidence of |
|-------------------|----|--------|----------|----------|------------------------|
| Observation group | 61 | 1      | 1        | 2        | 4(6.56)                |
| Control group     | 59 | 2      | 2        | 1        | 5(8.47)                |
| $\chi^2$ value    |    |        |          |          | 0.159                  |
| P value           |    |        |          |          | 0.690                  |

### 3 讨论

2型糖尿病是以持续性血糖上升、胰岛素抵抗和胰岛功能分泌受损为特点的代谢性疾病,占糖尿病的90%以上,伴有糖、脂肪、蛋白质等代谢紊乱<sup>[10,11]</sup>。目前,临床治疗2型糖尿病主要采用二甲双胍治疗,可降低糖尿病患者空腹血糖,增加周围组织对胰岛素抵抗的敏感性,提高葡萄糖的利用率,抑制肝糖原异生和肝糖输出,进而改善胰岛素抵抗,但部分患者单一采用二甲双胍的治疗效果不佳,且部分胃肠道耐受性差且低灌注水平的患者,存在一定肾功能损害风险<sup>[13-16]</sup>。达格列净是一种新型的降糖药物,是首个钠-葡萄糖协同转运蛋白2抑制剂,可通

过抑制肾小管重吸收葡萄糖促进尿糖排泄,在不引起低血糖的同时降低患者血糖水平<sup>[17-19]</sup>。对单用二甲双胍控制不佳的2型糖尿病患者,联合达格列净减少低血糖的风险,同时可控制体质质量<sup>[20]</sup>。本研究结果显示联合达格列净治疗的患者总有效率为93.62%,明显高于单独使用二甲双胍治疗的患者,提示达格列净联合二甲双胍可提高2型糖尿病患者的治疗效果。Yunes Panahi<sup>[21]</sup>等研究显示达格列净能综合调节患者体内代谢,缓解2型糖尿病患者血管并发症,降低心血管事件的发生率。本研究结果显示两组患者治疗期间不良反应发生率无明显差异,Joana F. Sacramento<sup>[22]</sup>等研究也显示达格列净可通过尿液排糖,减少发生低血糖事件。分析其原因可能是因为二甲双胍可增加

胰岛素介导的葡萄糖利用,增加对葡萄糖的利用,降低肝糖输出;达格列净作为钠-葡萄糖协同转运蛋白2抑制剂可减轻体重,改善多种代谢指标,两组药物联合治疗可提高治疗效果,减少不良反应。

研究表明糖脂代谢紊乱、氧化应激与2型糖尿病的发生密切相关<sup>[23]</sup>。2型糖尿病的发生可导致患者出现高血糖状态,从而抑制一氧化氮自由基的形成,促进葡萄糖和脂质氧化反应,而抗氧化剂与胰岛素共同作用促进一氧化氮自由基,减少葡萄糖和脂质氧化反应;同时,糖脂代谢紊乱则会引起血管壁沉淀物增多,造成内皮功能损伤,促进基底膜增厚,从而增加并发症<sup>[24-27]</sup>。因此,改善患者糖脂代谢紊乱对2型糖尿病的治疗具有重要意义。FBG、FINS、HbA1c是糖代谢常用指标,TC、TG、LDL-C、HDL-C是反映脂代谢常用指标,LDL-C、HDL-C属载脂蛋白,LDL-C是血液内转运的一种形式,主要是转运内源性胆固醇,可将脂类由肝脏向外转运;HDL-C是逆向转运胆固醇,主要将脂类由外周转运至肝脏分解代谢<sup>[28-31]</sup>。本研究结果显示观察组治疗后FBG、FINS、HbA1c、TC、TG、LDL-C水平均显著低于对照组,HDL-C水平显著高于对照组,提示达格列净联合二甲双胍可改善2型糖尿病患者糖脂代谢水平。Azam Rezaei Farimani<sup>[32]</sup>等研究也显示在常规治疗基础上联合达格列净可有效改善2型糖尿病患者代谢异常指标。分析其原因可能是因为二甲双胍可增加周围组织对胰岛素敏感,抑制肝糖原异生,抑制葡萄糖吸收;达格列净可抑制近端肾小管葡萄糖重吸收,促进葡萄糖从尿液中排泄而降糖的同时增强肝脏及肌肉等敏感性,进而降低患者血糖及胰岛素水平。

胰岛素抵抗是指各种原因使胰岛素促进葡萄糖摄取和利用的效率下降,机体代偿性的分泌过多胰岛素产生高胰岛素血症,以维持血糖的稳定<sup>[33,34]</sup>。胰岛素抵抗贯穿2型糖尿病整个发展过程<sup>[35]</sup>,HOMA- $\beta$ 是反映胰岛素敏感性的重要指标,HOMA- $\beta$ 下降提示糖尿病患者体细胞对于胰岛素受体敏感性的下降。本研究结果显示观察组治疗后HOMA- $\beta$ 显著高于对照组,HOMA-IR显著低于对照组,提示达格列净联合二甲双胍可改善2型糖尿病患者胰岛素功能。联合达格列净不仅可促进葡萄糖排除降血糖,还可增强肝脏等组织胰岛素敏感性,从而降低患者胰岛素水平。分析其原因可能是因为二甲双胍可增加周围组织对胰岛素的敏感性,提高胰岛素介导的葡萄糖利用,抑制肠壁细胞摄取葡萄糖;达格列净可促进葡萄糖排除降血糖,增强肝脏及肌肉等组织胰岛素敏感性,进而降低患者血糖及胰岛素水平。

综上所述,达格列净联合二甲双胍治疗2型糖尿病的效果显著优于单用二甲双胍治疗,其可有效改善患者糖脂代谢水平,且不会增加不良反应。

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