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## 血糖变异性对 2 型糖尿病合并冠心病患者近期心血管事件的影响

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**[摘要]** 目的：分析血糖变异性对2型糖尿病(type2 diabetes mellitus, T2DM)合并冠心病患者近期心血管事件的影响。方法：选取2015年6月至2018年4月河南科技大学第一附属医院收治的T2DM患者120例为研究对象，依据冠状动脉造影结果将其分为对照组(单纯糖尿病, n=48)、观察组(糖尿病合并冠心病, n=72)，记录入院72 h动态血糖监测结果，对比其一般资料、空腹血糖(FPG)及糖化血红蛋白(HbA1c)水平、血糖变异性参数[全天血糖平均值(mean blood glucose, MBG)、日内最大血糖波动幅度(largest amplitude of glycemic excursion, LAGE)、全天血糖标准差(standard deviation of blood glucose, SDBG)、日间血糖平均绝对差(mean of daily differences, MODD)、平均餐后血糖漂移幅度(mean postprandial glucose excursion, MPPGE)、空腹血糖变异系数(coefficient of variation of fasting plasma glucose, CV-FPG)]、心血管事件的差异，分析各指标对近期心血管事件的风险比。结果：观察组FPG, HbA1c、尿酸、超敏C反应蛋白(hs-CRP)水平高于对照组，左室射血分数(left ventricular ejection fraction, LVEF)低于对照组( $P<0.05$ )，而其他资料比较差异无统计学意义( $P>0.05$ )；观察组LAGE, SDBG, MODD, MPPGE, CV-FPG高于对照组( $P<0.01$ )，两组MBG比较差异无统计学意义( $P>0.05$ )；观察组近期心血管事件发生率高于对照组( $P<0.05$ )；Cox回归分析显示，随诊期间HbA1c, FPG水平及LAGE, SDBG, MODD, MPPGE, CV-FPG均影响T2DM合并冠心病患者近期心血管事件的发生( $P<0.05$ )，尤其是LAGE, MODD, MPPGE的影响程度更大( $P<0.01$ )。结论：血糖变异性可影响T2DM合并冠心病患者近期心血管事件的发生，应加以监测。

**[关键词]** 血糖变异性；2型糖尿病；冠心病；心血管事件

## Effect of glucose variability on recent cardiovascular events in patients with type 2 diabetes mellitus combined with coronary heart disease

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**Abstract** **Objective:** To analyze the effect of glucose variability on recent cardiovascular events in patients with type 2 diabetes mellitus (T2DM) combined with coronary heart disease. **Methods:** A total of 120 patients with T2DM in the hospital from June 2015 to April 2018 were selected as the study subjects. According to the results of coronary

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angiography, they were divided into control group (diabetes mellitus,  $n=48$ ) and observation group (diabetes mellitus combined with coronary heart disease,  $n=72$ ). The results of continuous glucose monitoring in 72 h after admission were recorded. The general data, fasting plasma glucose (FPG) and glycosylated hemoglobin (HbA1c) levels, glucose variability parameters [mean blood glucose (MBG), largest amplitude of glycemic excursion (LAGE), standard deviation of blood glucose (SDBG), means of daily differences (MODD), mean postprandial glucose excursion (MPPGE), coefficient of variation of fasting plasma glucose (CV-FPG)] and differences in cardiovascular events were compared between the two groups. The risk ratio of each indicator to recent cardiovascular events was analyzed. **Results:** The levels of FPG, HbA1c, uric acid and high-sensitivity C-reactive protein (hs-CRP) in the observation group were higher than those in the control group, while LVEF was lower than that in the control group ( $P<0.05$ ). There was no significant difference in other data between the two groups ( $P>0.05$ ). The LAGE, SDBG, MODD, MPPGE and CV-FPG in the observation group were higher than those in the control group ( $P<0.01$ ). There was no significant difference in MBG between the two groups ( $P>0.05$ ). The incidence of recent cardiovascular events in the observation group was higher than that in the control group ( $P<0.05$ ). Cox regression analysis showed that HbA1c and FPG levels, LAGE, SDBG, MODD, MPPGE and CV-FPG affected the occurrence of recent cardiovascular events in patients with T2DM and coronary heart disease during follow-up ( $P<0.05$ ). In particular, the effect degree of LAGE, MODD and MPPGE was greater ( $P<0.01$ ). **Conclusion:** Glucose variability can affect the occurrence of recent cardiovascular events in patients with T2DM and coronary heart disease. It should be monitored.

**Keywords** glucose variability; type 2 diabetes mellitus; coronary heart disease; cardiovascular event

随我国人口老龄化加速及人们生活方式改变, 糖尿病发生率呈上升趋势, 其中2型糖尿病(type 2 diabetes mellitus, T2DM)是糖尿病常见类型<sup>[1]</sup>。临床已经明确糖化血红蛋白(HbA1c)作为血糖平均水平的指标与糖尿病慢性并发症风险呈正相关, 但其在反映血糖控制情况上仍有一定局限性, 多数HbA1c<7%的患者仍有不同程度并发症出现<sup>[2-3]</sup>。而血糖变异性又称为血糖波动性, 其是血糖水平在峰值与谷值之间震荡的非稳定状态, 既包括一日内血糖变化, 也包括一段时期内血糖变化<sup>[4-5]</sup>。近年来血糖变异性与心、脑血管疾病的关系愈演愈烈, 不仅与冠状动脉病变程度相关, 也影响心血管疾病预后, 同时能预测心血管疾病发生风险。糖尿病为冠心病发生的危险因素, 冠心病患者中血糖异常者高达76.9%<sup>[6]</sup>, 然而关于血糖变异性对T2DM合并冠心病患者心血管事件的影响报道甚少。本文主要评估血糖变异性对T2DM合并冠心病患者近期心血管事件的影响, 现报告如下。

## 1 对象与方法

### 1.1 对象

选取2015年6月至2018年4月河南科技大学第一附属医院收治的T2DM患者120例, 纳入标

准: 1)符合《中国2型糖尿病防治指南(2013年版)》<sup>[7]</sup>中T2DM诊断标准, T2DM病程达3个月以上者; 2)HbA1c在6.5%~13.0%, 近3个月内未改变降糖方案者; 3)近1个月内无急性心肌梗死或肝肾等重要脏器功能异常, 同意参与本研究并进行冠状动脉造影术者。排除标准: 1)合并严重肝肾功能不全、甲状腺功能亢进或自身免疫性疾病者; 2)过度肥胖、急性冠脉综合征、急性代谢紊乱及感染者; 3)近1周内服用过非甾体抗炎药或类固醇药物及其他应激情况者。依据冠状动脉造影结果将其分为对照组(单纯糖尿病,  $n=48$ )、观察组(糖尿病合并冠心病,  $n=72$ ), 两组一般资料见表1。本研究经河南科技大学第一附属医院医学伦理委员会批准, 患者均签署知情同意书。

### 1.2 方法

#### 1.2.1 一般资料收集、生化指标测定及冠心病的诊断

入院后采集患者一般资料, 包括性别、年龄、T2DM病程、吸烟史、高血压、脑卒中史等, 并测量收缩压(systolic blood pressure, SBP)、舒张压(diastolic blood pressure, DBP)、身高、体质指数(body mass index, BMI)。在入院后次日(空腹禁食>10 h)抽取静脉血, 以日本日立公司提供的7600型自动生化分析仪测定生化指标[空腹血糖(fasting

blood sugar, FPG)、血脂、尿酸、超敏C反应蛋白(hypersensitive C-reactive protein, hs-CRP)], 应用离子交换高效液相法(试剂盒由美国Bio-Rad公司提供)测定HbA1c, 采用超声心动图测定左室射血分数(left ventricular ejection fraction, LVEF)。于入院后5~7 d行冠状动脉造影术, 以Philips数字减影血管造影机经桡动脉选择性进行冠状动脉造影, 造影发现左主干、左前降支、右回旋支、右冠状动脉中任意一支血管狭窄≥50%则判定为冠心病, 心外膜冠状动脉狭窄程度在50%以下则判定为不合并冠心病。

### 1.2.2 血糖水平测定及血糖变异性评估

入院后次日采用美国Medtronic MiniMed公司提供的CGMS血糖仪连续72 h持续动态监测血糖, 以皮下组织间液葡萄糖浓度反映血糖水平, 有效监测范围为2.2~22.2 mmol/L, 每天至少测定4次指端血糖进行矫正, 每24 h获得288个测定

值, 监测期间不调整降糖方案, 不改变饮食、活动情况。血糖变异性参数: 全天血糖平均值(mean blood glucose, MBG)为受试者24 h连续监测期间共288个测定值的平均值, 日内最大血糖波动幅度(largest amplitude of glycemic excursion, LAGE): 受试者24 h监测期间最大值及最小值之差, 全天血糖标准差(standard deviation of blood glucose, SDBG): 受试者CGMS 24 h监测期间共288个测定值的标准差, 日间血糖平均绝对差(absolute mean of daily differences, MODD): 受试者2个连续24 h监测期间CGMS相匹配测定值间的平均绝对差, 平均餐后血糖漂移幅度(mean amplitude glycemic excursions, MPPGE): 三餐后3 h最高血糖值与餐前血糖差值绝对值的平均数, 空腹血糖变异系数(coefficient of variation of fasting blood sugar, CV-FPG): 受试者CGMS 24 h监测期间共288个测定值的标准差除以24 h平均FPG。

**表1 两组一般资料及生化指标、血糖监测水平比较**

**Table 1 Comparison of general data, biochemical indicators and blood glucose monitoring levels between the two groups**

| 组别         | n           | 性别/[例(%)]                    |                              | 年龄/岁                       | T2DM病程/月                     | 吸烟史/[例(%)]                  | 高血压史/[例(%)] |
|------------|-------------|------------------------------|------------------------------|----------------------------|------------------------------|-----------------------------|-------------|
|            |             | 男                            | 女                            |                            |                              |                             |             |
| 观察组        | 72          | 38 (52.78)                   | 34 (47.22)                   | 59.63 ± 6.07               | 102.15 ± 11.37               | 25 (34.72)                  | 17 (23.61)  |
| 对照组        | 48          | 26 (54.17)                   | 22 (45.83)                   | 60.15 ± 6.12               | 99.12 ± 10.23                | 18 (37.50)                  | 10 (20.83)  |
| $\chi^2/t$ |             | 0.223                        |                              | 0.458                      | 1.488                        | 0.097                       | 0.127       |
| P          |             | 0.881                        |                              | 0.648                      | 0.139                        | 0.756                       | 0.721       |
| 组别         | 脑卒中史/[例(%)] | SBP/mmHg                     | DBP/mmHg                     | 身高/cm                      | BMI/(kg·m <sup>-2</sup> )    | FPG/(mmol·L <sup>-1</sup> ) |             |
| 观察组        | 14 (19.44)  | 137.78 ± 13.96               | 81.24 ± 8.37                 | 169.45 ± 17.24             | 25.44 ± 2.63                 | 8.45 ± 0.85                 |             |
| 对照组        | 9 (18.75)   | 138.59 ± 14.15               | 82.65 ± 8.30                 | 170.11 ± 17.68             | 25.37 ± 2.60                 | 7.29 ± 0.76                 |             |
| $\chi^2/t$ | 0.009       | 0.310                        | 0.907                        | 0.203                      | 0.143                        | 7.635                       |             |
| P          | 0.925       | 0.757                        | 0.366                        | 0.839                      | 0.886                        | <0.001                      |             |
| 组别         | HbA1c/%     | 总胆固醇/(mmol·L <sup>-1</sup> ) | 三酰甘油/(mmol·L <sup>-1</sup> ) | 尿酸/(mmol·L <sup>-1</sup> ) | hs-CRP/(mg·L <sup>-1</sup> ) | LVEF/%                      |             |
| 观察组        | 7.89 ± 0.83 | 4.57 ± 0.52                  | 2.35 ± 0.24                  | 289.54 ± 29.11             | 10.45 ± 1.18                 | 55.43 ± 5.66                |             |
| 对照组        | 7.54 ± 0.80 | 4.51 ± 0.46                  | 2.29 ± 0.25                  | 246.48 ± 25.37             | 6.43 ± 0.68                  | 62.14 ± 6.37                |             |
| $\chi^2/t$ | 2.296       | 0.648                        | 1.319                        | 8.348                      | 21.340                       | 6.049                       |             |
| P          | 0.023       | 0.518                        | 0.190                        | <0.001                     | <0.001                       | <0.001                      |             |

1 mmHg=0.133 kPa.



表4 血糖水平及血糖变异性对心血管事件发生的影响

Table 4 Risk ratio of the effects of blood glucose levels and glucose variability on cardiovascular events

| 因素     | $\beta$ | SE    | IR    | 95%CI       | P      |
|--------|---------|-------|-------|-------------|--------|
| HbA1c  | 0.254   | 0.123 | 1.289 | 1.013~1.641 | 0.040  |
| FPG    | 0.158   | 0.067 | 1.171 | 1.027~1.336 | 0.019  |
| LAGE   | 0.457   | 0.164 | 1.579 | 1.145~2.178 | 0.006  |
| SDBG   | 0.268   | 0.107 | 1.307 | 1.060~1.612 | 0.013  |
| MODD   | 0.399   | 0.099 | 1.490 | 1.227~1.809 | <0.001 |
| MPPGE  | 0.415   | 0.134 | 1.514 | 1.165~1.969 | 0.002  |
| CV-FPG | 0.354   | 0.120 | 1.425 | 1.126~1.803 | 0.003  |

### 3 讨论

糖尿病发生时，机体脂代谢及凝血系统会发生功能异常，引起内皮细胞功能障碍及血管炎症，促进动脉粥样硬化及血栓形成，在长期糖尿病患者中发生冠心病危险性将会上升<sup>[8]</sup>。血糖变异性指血糖水平在高值及低值间变化的非稳定状态，近年来研究<sup>[9-10]</sup>发现：血糖变异性与糖尿病并发症的发生发展密切相关，血糖变异性为一个可独立预测危重症患者死亡的重要预后因子，其预测价值可能超过高血糖本身作用，血糖变异性越大，其对心、脑、肾等重要脏器的影响也就越大。

方圆圆等<sup>[11]</sup>研究发现：T2DM患者血糖变异性与冠状动脉狭窄程度有密切关系，其中餐后血糖变异性为冠脉狭窄程度的独立预测因素。何泉等<sup>[12]</sup>指出：T2DM合并急性冠状动脉综合征急性期血糖变异性可能使血管生成素2升高及内质网应激增加，还与心脏收缩功能有关，前期研究均表明血糖变异性可能参与T2DM合并冠心病发生发展。本研究对比了72例T2DM合并冠心病患者、48例单纯T2DM患者的临床资料及入院时血糖等生化指标检测结果，发现观察组FPG, HbA1c, 尿酸, hs-CRP水平高于对照组，LVEF低于对照组，两组T2DM病程、血压、BMI、血脂等指标比较差异无显著性，表明T2DM合并冠心病患者相比于单纯T2DM患者其血糖水平可能上升更显著，在病程、血压、血脂、BMI等控制相当情况下，血糖水平可能在一定程度上加剧冠状动脉病变进程，增加炎症反应及心功能损伤。

血糖变异性中MAGE被认为是评估日内血糖波动的代表性指标，其不依赖于平均血糖值，用

来量化24 h内主要血糖波动，而MPPGE则反映餐后血糖波动，是T2DM患者血糖波动的主要贡献者，MODD则是评价日间血糖波动的唯一参数，不依赖于日内血糖波动，独立反映不同日间血糖波动，CV-FPG则反映血糖离散程度，也反映血糖波动情况<sup>[13-14]</sup>。本研究中观察组的LAGE, SDBG, MODD, MPPGE, CV-FPG均较对照组高，而两组MBG比较差异无统计学意义，这与温晨东等<sup>[15]</sup>的研究结果相近，证实在血糖水平控制相当情况下，血糖波动幅度可能在一定程度上促进冠状动脉狭窄病变进展，原因可能为血糖慢性波动增加胰岛素抵抗，参与动脉粥样硬化发展，慢性血糖波动也可能引发氧化应激反应，增加内皮功能障碍、凝血纤溶系统功能障碍及自由基产生，加速动脉粥样硬化形成。此外慢性血糖波动也会减弱葡萄糖浓度状态下细胞经调节性反馈以部分拮抗葡萄糖毒性作用，促进细胞形态及功能受损<sup>[16]</sup>。

血糖变异性与心血管事件的关系在近年来受到关注。郜琳等<sup>[17]</sup>研究发现：高龄冠心病合并T2DM患者餐后2 h血糖水平上升将增加心血管事件发生率，尤其是心梗发生率。本研究中观察组近期急性心梗、充血性心力衰竭、频发心绞痛、冠脉搭桥、严重心律失常等心血管事件发生率高于对照组，表明T2DM合并冠心病者较单纯T2DM者有更高的心血管事件发生风险，而本研究进一步Cox回归分析显示：随诊期间HbA1c, FPG水平及LAGE, SDBG, MODD, MPPGE, CV-FPG均影响T2DM合并冠心病患者近期心血管事件的发生，尤其是LAGE, MODD, MPPGE的影响程度更大，这与刘伯芹等<sup>[18]</sup>经过研究得出的随诊间HbA1c, FPG变异性及平均HbA1c, FPG水平影响心脑血管事件的发生，且HbA1c, FPG变异性对心脑血

管事件发生的影响不依赖于平均血糖水平的结果相近,这也是本研究两组MBG相似,而HbA1c, FPG有差异的原因。血糖波动可经过不同代谢途径导致大血管及微血管病变,急性高血糖对心血管的危害是通过大量自由基产生而发挥作用,部分炎性反应、细胞因子及黏附分子分泌表达异常可能增加内皮细胞凋亡,使血管硬化,而反复波动的高糖环境较持续稳定的高糖环境对内皮细胞形态及功能的损害更严重,此外血糖变异性改变可降低内皮细胞NO生成,引起血管舒张功能障碍,加重活性氧对血管内皮线粒体损害及血管炎性反应,因此LAGE, MODD, MPPGE值越高,血糖波动越大,对心血管事件的影响更大,这对T2DM合并冠心病等并发症的发生、发展起推动作用<sup>[19]</sup>。Tang等<sup>[20]</sup>通过对240例无心血管疾病的T2DM患者进行SDBG, MPPGE, MODD等参数进行监测,也发现血糖变异性为HbA1c控制良好(≤7.0%)的T2DM患者10年心血管疾病风险的独立预测因子。

综上所述,血糖变异性可能增加T2DM合并冠心病患者近期心血管事件发生风险,因此在血糖出现异常时积极予以降糖治疗同时应重视血糖变异性的改变,连续动态监测血糖,有效控制血糖波动对靶器官的损害,避免终点事件的发生。

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