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2 型糖尿病患者血糖波动与心律失常和下肢血管病变的关系及其影响因素分析 *

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摘要 目的:探讨 2 型糖尿病(T2DM)患者血糖波动与心律失常和下肢血管病变的关系,分析影响 T2DM 心律失常和下肢血管病变的因素。**方法:**选择 2019 年 7 月到 2020 年 6 月我院收治的 82 例 T2DM 患者,根据是否合并心律失常分为心律失常组 28 例和无心律失常组 54 例,根据是否合并下肢血管病变分为下肢血管病变组 31 例和无下肢血管病变组 51 例。所有患者均通过 72 h 监测血糖获得日内平均血糖波动幅度(MAGE)、日间血糖平均绝对差(MODD)、全天血糖标准差(SDBG)、全天血糖波动次数(NGE)。比较组间差异,分析影响 T2DM 患者心律失常和下肢血管病变的因素。**结果:**心律失常组 MAGE、MODD、SDBG、NGE、糖化血红蛋白(HbA1c)、胰岛素抵抗指数(HOMA-IR)、T2DM 病程、同型半胱氨酸(Hcy)、丙二醛(MDA)高于无心律失常组($P<0.05$)。下肢血管病变组 T2DM 病程、Hcy、MDA、HOMA-IR、MAGE、MODD、SDBG、NGE 均高于无下肢血管病变组($P<0.05$)。Logistic 回归分析结果显示 MDA、HOMA-IR、MAGE、MODD 是 T2DM 患者心律失常的危险因素($P<0.001$),MAGE、MODD、SDBG 是 T2DM 患者下肢血管病变的危险因素($P<0.001$)。**结论:**T2DM 患者血糖波动与心律失常和下肢血管病变均有关,血糖波动增加是 T2DM 心律失常和下肢血管病变的危险因素。

关键词:2 型糖尿病;血糖波动;心律失常;下肢血管病变;影响因素

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Relationship between Blood Glucose Fluctuation and Arrhythmia and Lower Extremity Vascular Lesions in Patients with Type 2 Diabetes Mellitus and Its Influencing Factors*

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ABSTRACT Objective: To investigate the relationship between blood glucose fluctuation and arrhythmia and lower extremity vascular lesions in patients with type 2 diabetes mellitus (T2DM), and to analyze the influencing factors the arrhythmia and lower extremity vascular lesions in T2DM. **Methods:** A total of 82 patients with T2DM who were admitted to our hospital from July 2019 to June 2020 were selected. According to the presence or absence of arrhythmia, the patients were divided into arrhythmia group (28 cases) and non arrhythmia group (54 cases). According to the presence or absence of lower extremity vascular disease, they were divided into lower extremity vascular lesions group (31 cases) and non lower extremity vascular lesions group (51 cases). The average amplitude of intra-day blood glucose fluctuation (MAGE), the average absolute difference of daytime blood glucose (MODD), the standard deviation of all-day blood glucose (SDBG), and the number of all-day blood glucose fluctuation (NGE) were obtained by monitoring blood glucose for 72h. The differences between groups were compared, and the factors affecting arrhythmia and lower extremity vascular lesions in patients with T2DM were analyzed. **Results:** MAGE, MODD, SDBG, NGE, glycosylated hemoglobin (HbA1c), insulin resistance index (HOMA-IR), T2DM course, homocysteine (Hcy), malondialdehyde (MDA) in the arrhythmia group were higher than those in the non arrhythmia group ($P<0.05$). The T2DM course, Hcy, MDA, HOMA-IR, MAGE, MODD, SDBG and NGE in the lower extremity vascular lesions group were all higher than those in the non lower extremity vascular lesions group ($P<0.05$). Logistic regression analysis showed that MDA, HOMA-IR, MAGE and MODD were risk factors for arrhythmia in patients with T2DM ($P<0.001$), MAGE, MODD and SDBG were risk factors for lower extremity vascular lesions in patients with T2DM ($P<0.001$). **Conclusion:** Blood glucose fluctuation in patients with T2DM is related to arrhythmia and lower extremity vascular lesions, and increased blood glucose fluctuation is a risk factor for arrhythmia of T2DM and lower extremity vascular lesions.

Key words: Type 2 diabetes; Glucose fluctuation; Arrhythmology; Lower extremity vascular lesions; Influencing factors

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前言

2型糖尿病(T2DM)是继肿瘤、心血管疾病之后死亡率排名第3的非传染性疾病^[1],我国最新统计数据显示成年人T2DM患病率达10.4%^[2]。T2DM是心血管疾病的危险因素,T2DM糖代谢异常介导的微血管以及心肌病变改变心肌传导系统,引起交感神经兴奋,迷走神经活性降低,缩短心肌细胞不应期,导致心律失常^[3]。血糖异常波动较高血糖对心血管系统的影响更大,是心血管疾病预后不良的危险因素^[4],血糖波动与心律失常成为临床研究热点^[5]。下肢血管病变是T2DM致残致死性并发症^[6],传统观念认为高血糖水平,糖化血红蛋白(HbA1c)控制不良与下肢血管病变有关^[7],随着血糖波动监测技术的问世和推广,发现血糖波动增强可加重血管内皮损伤,促进下肢血管疾病的发生发展^[8,9]。本研究通过探讨血糖波动与T2DM患者心律失常和下肢血管病变的关系,分析血糖波动对心律失常和下肢血管病变的影响。

1 资料与方法

1.1 临床资料

选择2019年7月到2020年6月我院收治的82例T2DM患者,根据是否合并心律失常分为心律失常组28例和无心律失常组54例,根据是否合并下肢血管病变分为下肢血管病变组31例和无下肢血管病变组51例。纳入标准:①符合2017年版T2DM防治指南^[2];②T2DM病程1年以上;③近三个月未服用抗心律失常药物;④所有患者均知情且签署同意书。排除标准:①1型糖尿病、妊娠期糖尿病;②下肢创伤或手术;③T2DM确诊前已经明确诊断的心律异常或器质性心脏病;④合并急性感染者。下肢血管病变诊断标准^[10]:①静息踝臂指数(ABI)≤0.90;②运动后ABI下降15%~20%或运动时下肢不适且静息ABI≥0.90,符合上述任何一项可诊断为下肢血管病变。心律失常诊断标准^[10]:24小时动态心电图提示窦性心动过速、房早、室早、室速、房速、房颤、室颤、房室传导阻滞等。本研究获得我院伦理委员会批准。

1.2 血糖波动

所有患者入院后维持原降糖方案,动态血糖监测系统(美国雅培公司),埋置感应探头于皮下记录血糖值,连续监测72h,每天输入4次指尖血糖校正探头信息,每天记录288个血糖值。记录血糖波动参数:日内平均血糖波动幅度(MAGE)、日间血糖平均绝对差(MODD)、全天血糖标准差(SDBG)、全天血糖波动次数(NGE)。

1.3 临床资料收集

收集患者年龄、性别、T2DM病程、收缩压、舒张压、体质量(BMI)、生化指标[西门子ADVIA2400全自动生化分析仪检测总胆固醇(TC)、甘油三酯(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)、同型半胱氨酸(Hcy)、丙二醛(MDA)水平,PDQ PLUS糖化血红蛋白检测仪检测HbA1c,胰岛素抵抗指数(HOMA-IR)=(空腹血糖)×空腹

胰岛素/22.5]。

1.4 统计学分析

SPSS 25.0 进行数据分析,计量资料以($\bar{x} \pm s$)表示采用独立样本t检验,以率(%)表示计数资料采用 χ^2 检验。Logistic回归分析影响T2DM患者心律失常和下肢血管病变的因素。所有统计均采用双侧检验,检验水准 $\alpha=0.05$ 。

2 结果

2.1 有无心律失常患者血糖波动参数、临床指标比较

心律失常组MAGE、MODD、SDBG、NGE、HbA1c、HOMA-IR、T2DM病程、Hcy、MDA高于无心律失常组($P<0.05$),两组年龄、性别、收缩压、舒张压、BMI、TC、TG、LDL-C、HDL-C比较无统计学差异($P>0.05$),见表1。

2.2 有无下肢血管病变患者血糖波动参数、临床指标比较

下肢血管病变组T2DM病程、Hcy、MDA、HOMA-IR、MAGE、MODD、SDBG、NGE均高于无下肢血管病变组($P<0.05$),两组年龄、性别、收缩压、舒张压、BMI、TC、TG、LDL-C、HDL-C、HbA1c比较无统计学差异($P>0.05$),见表2。

2.3 影响T2DM患者心律失常的因素分析

以心律失常为因变量构建Logistic回归模型,代入自变量MAGE、MODD、SDBG、NGE、HbA1c、HOMA-IR、T2DM病程、Hcy、MDA,逐步法排除无关变量(入 $\alpha=0.05$,出 $\alpha=0.1$),结果MDA、HOMA-IR、MAGE、MODD是T2DM患者心律失常的危险因素($P<0.001$),见表3。

2.4 影响T2DM患者下肢血管病变的因素分析

以下肢血管病变为因变量构建Logistic回归模型,代入自变量T2DM病程、Hcy、MDA、HOMA-IR、MAGE、MODD、SDBG、NGE,逐步法排除无关变量(入 $\alpha=0.05$,出 $\alpha=0.1$),结果MAGE、MODD、SDBG是T2DM患者下肢血管病变的危险因素($P<0.001$),见表4。

3 讨论

T2DM心血管并发症是导致患者致死致残的首要原因,波动性高血糖时心律失常的发生及其机制比持续性高血糖更为复杂^[11-13]。Su JB等^[14]观察T2DM患者血糖波动、慢性持续性高血糖对QT间期的影响,发现QT间期延长患者FPG、PPG标准差和平均值高于QT间期正常者,QT间期延长与FPG、PPG标准差和平均值呈正相关。本研究结果显示心律失常组MAGE、MODD、SDBG、NGE高于无心律失常组,MAGE、MODD与心律失常的发生相关,提示血糖波动是引起T2DM患者心律失常的危险因素之一。血糖波动引起心律失常的机制可能是:首先,血糖波动可诱导机体氧化应激反应,导致氧自由基和活性氧生成增加,损害冠脉内皮细胞,引起心电活动不稳定,影响心肌传导系统,易诱发心律失常等^[15-17]。动物实验研究发现血糖波动可上调硫氧还蛋白互作蛋白和还原型烟酰胺腺嘌呤二核苷酸磷酸氧化酶表达,引起活性氧水平升高,诱导心肌纤维化,导致心律失常发生^[18]。其次,炎症反应也参与血管内

表 1 有无心律失常患者血糖波动参数、临床指标比较($\bar{x} \pm s$)Table 1 Comparison of blood glucose fluctuation parameters and clinical indexes in patients with or without arrhythmia($\bar{x} \pm s$)

Groups	Arrhythmia group(n=28)	Non arrhythmia group(n=54)	t/χ^2	P
Age(years old)	61.75±4.83	61.02±4.91	0.533	0.596
Male/female	19/9	34/20	0.193	0.660
T2DM course(years)	9.17±2.92	7.64±2.31	2.041	0.047
Systolic blood pressure(mmHg)	139.46±9.56	138.05±9.11	0.535	0.595
Diastolic blood pressure(mmHg)	78.34±6.19	78.15±6.09	0.110	0.913
BMI(kg/m ²)	24.89±3.29	24.84±3.17	0.055	0.956
TC(mmol/L)	4.92±0.42	4.71±0.39	1.834	0.073
TG(mmol/L)	2.56±0.53	2.51±0.57	0.324	0.747
LDL-C(mmol/L)	2.94±0.49	2.71±0.43	1.761	0.084
HDL-C(mmol/L)	2.15±0.65	2.06±0.57	0.520	0.606
Hcy(μ mol/L)	11.76±3.69	9.52±2.41	2.503	0.016
MDA(nmol/L)	7.24±0.69	5.12±0.63	11.350	0.000
HbA1c(%)	9.25±0.35	8.94±0.32	3.270	0.002
HOMA-IR	3.95±0.39	3.02±0.28	9.580	0.000
MAGE(mmol/L)	7.21±2.16	5.32±0.69	4.025	0.000
MODD(mmol/L)	3.16±0.69	1.85±0.35	8.264	0.000
SDBG(mmol/L)	2.81±0.53	2.23±0.45	4.158	0.000
NGE(times/d)	3.96±0.73	2.71±0.52	6.895	0.000

表 2 有无下肢血管病变患者血糖波动参数、临床指标比较($\bar{x} \pm s$)Table 2 Comparison of blood glucose fluctuation parameters and clinical indexes in patients with or without lower extremity vascular lesions($\bar{x} \pm s$)

Groups	Lower extremity vascular lesions group (n=31)	Non lower extremity vascular lesions group (n=51)	t/χ^2	P
Age(years old)	61.38±5.26	61.20±4.96	0.156	0.877
Male/female	20/11	33/18	0.097	0.756
T2DM course(years)	10.24±2.13	6.90±1.36	8.766	0.000
Systolic blood pressure(mmHg)	139.06±9.46	138.21±8.34	0.425	0.672
Diastolic blood pressure(mmHg)	78.65±6.59	77.95±5.31	0.528	0.599
BMI(kg/m ²)	25.13±3.26	24.69±2.95	0.629	0.531
TC(mmol/L)	4.82±0.35	4.76±0.32	0.795	0.429
TG(mmol/L)	2.59±0.61	2.50±0.48	0.412	0.681
LDL-C(mmol/L)	2.84±0.49	2.76±0.41	0.795	0.429
HDL-C(mmol/L)	2.11±0.63	2.08±0.53	0.231	0.818
Hcy(μ mol/L)	13.26±4.11	8.48±2.56	6.499	0.000
MDA(nmol/L)	6.83±0.84	5.24±0.59	10.05 4	0.000
HbA1c(%)	9.07±0.36	9.03±0.33	0.514	0.609
HOMA-IR	3.77±0.42	3.07±0.29	7.482	0.000
MAGE(mmol/L)	7.12±0.65	5.26±0.58	8.369	0.000
MODD(mmol/L)	3.62±0.74	1.49±0.31	9.082	0.000
SDBG(mmol/L)	2.86±0.67	2.17±0.36	4.259	0.000
NGE(times/d)	4.03±0.69	2.59±0.48	8.361	0.000

表 3 T2DM 患者心律失常影响因素的 Logistic 回归分析

Table 3 Logistic regression analysis of influencing factors of arrhythmia in T2DM patients

Factors	β	SE	Wald χ^2	OR(95%CI)	P
MAGE	0.645	0.231	7.796	1.906(1.843~2.116)	0.000
MODD	0.549	0.174	9.955	1.732(1.625~1.847)	0.000
SDBG	0.243	0.185	1.725	1.275(0.924~1.389)	0.715
NGE	0.213	0.174	1.499	1.237(0.902~1.362)	0.935
HbA1c	0.261	0.185	1.990	1.298(0.937~1.392)	0.635
HOMA-IR	0.463	0.175	7.000	1.589(1.495~1.685)	0.000
T2DM course	0.196	0.159	1.520	1.217(0.845~1.257)	0.864
Hcy	0.203	0.163	1.551	1.225(0.893~1.261)	0.832
MDA	0.483	0.163	8.780	1.621(1.536~1.783)	0.000

表 4 T2DM 患者下肢血管病变影响因素的 Logistic 回归分析

Table 4 Logistic regression analysis of influencing factors of lower extremity vascular disease in T2DM patients

Factors	β	SE	Wald χ^2	OR(95%CI)	P
MAGE	0.705	0.193	13.343	2.024(1.892~2.135)	0.000
MODD	0.692	0.182	14.457	1.998(1.845~2.064)	0.000
SDBG	0.685	0.205	11.165	1.984(1.845~2.036)	0.000
NGE	0.213	0.183	1.355	1.237(0.902~1.362)	0.953
MDA	0.196	0.162	1.464	1.217(0.895~1.253)	0.942
HOMA-IR	0.207	0.195	1.127	1.230(0.898~1.267)	0.978
T2DM course	0.183	0.163	1.260	1.201(0.865~1.248)	0.961
Hcy	0.173	0.153	1.279	1.189(0.843~1.206)	0.954

皮损伤过程,血糖波动幅度越大,炎症因子水平越高,炎症介质促使氧化应激反应产生,加重内皮损伤和心肌纤维化,引起心律失常^[19]。第三,血糖波动可引起多元醇旁路代谢加强^[20],诱发自主神经病变,兴奋交感神经,抑制迷走神经,导致心律失常。

糖尿病是下肢血管病变的主要危险因素之一^[21-23],全世界每 30 秒就有一例与糖尿病相关的下肢截肢,糖尿病占下肢血管病变患者行下肢截肢总病例数的 81.8%,75.6%的下肢截肢患者同时患有糖尿病和下肢血管病变^[24]。血糖波动是评价血糖控制水平的最重要参数之一,HbA1c 仅能反映过去 3 个月内的平均血糖水平,但不能反映血糖波动变化,HbA1c 控制相似的糖尿病患者,由于血糖波动程度不同,并发症发生的风险也不同^[25],血糖波动对糖尿病血管慢性并发症的影响比持续高血糖更大,是糖尿病血管疾病的重要预测因子。现有报道显示血糖波动是 T2DM 患者颈动脉内膜-中膜厚度增厚的独立危险因素^[26],在 T2DM 和急性心肌梗死患者中,血糖大幅波动与心血管疾病的发病率增加有关^[27],较高的血糖波动幅度与颈动脉斑块不稳定性增加有关^[28]。血糖波动也是 T2DM 下肢血管病变的病因和重要病理基础,MAGE、SDBG、LAGE、MODD 是评价血糖波动的常用参数,其中最具代表性的就是 MAGE。Zhang 等人^[28]报道指出 MAGE 与踝肱指数呈显著负相关,说明血糖波动水平与下肢血管病变程度有关。本研究同样发现下肢血管病变组 MAGE、MODD、SDBG、NGE 均高于无下肢血管病变

组,MAGE、MODD、SDBG 是 T2DM 患者下肢血管病变的危险因素,分析血糖波动参与下肢血管病变的机制为血管内皮功能障碍被认为是 T2DM 大血管并发症的病理基础,血糖波动会损伤血管内皮细胞,增加黏附分子的合成和分泌及其介导的黏附异常,激活氨基和多元醇途径,产生过量的末端糖基化产物,增加蛋白激酶 C 活性,导致下肢动脉粥样硬化^[30]。其次,血糖波动增大通过诱导氧化应激反应,损伤内皮细胞结构和功能,导致下肢血管病变的发生^[31]。稳定血糖波动水平,降低 MAGE、MODD、SDBG 可能会改善 T2DM 患者下肢血管病变程度^[32]。

综上所述,T2DM 患者血糖波动与心律失常和下肢血管病变均有关,血糖异常波动可能是导致 T2DM 心律失常和下肢血管病变的危险因素之一。血糖异常波动参数或许可以作为 T2DM 患者心律失常以及血管并发症评估的生物学指标。

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