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2 型糖尿病合并急性脑梗死患者血糖波动对体内氧化应激及炎症因子水平的影响及意义

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摘要 目的:探讨 2 型糖尿病(T2DM)合并急性脑梗死(ACI)患者血糖波动对体内氧化应激及炎症因子水平的影响及意义。**方法:**选取 2014 年 3 月到 2017 年 1 月第四军医大学唐都医院收治的 T2DM 合并 ACI 患者 100 纳入观察组,另选取同期在医院接受治疗的单纯 T2DM 患者 82 例作为对照组,比较两组患者的血糖水平标准差(SDBG)、日内平均血糖波动幅度(MAGE)、日间血糖波动幅度(MODD)、平均餐后血糖波动幅度(MPPGE)、丙二醛(MDA)、尿 8-异前列腺素 F_{2α}(8-iso-PGF_{2α})、肿瘤坏死因子 α(TNF-α)、超敏 C 反应蛋白(hs-CRP),并采用 Spearman 相关分析分析 MAGE 与 MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 的相关性。**结果:**观察组的 SDBG、MAGE、MPPGE、MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 均高于对照组,差异有统计学意义(P<0.05),两组的 MODD 比较差异无统计学意义(P>0.05)。经 Spearman 相关分析,MAGE 与 MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 均呈正相关(r=0.657, 0.732, 0.724, 0.538, P=0.013, 0.009, 0.010, 0.021)。**结论:**与单纯 T2DM 患者相比,T2DM 合并 ACI 患者存在较大的血糖波动,同时 MAGE 与患者体内的氧化应激及炎症因子水平呈正相关,临床上可通过控制血糖波动来降低患者的氧化应激反应程度及炎症因子水平,以改善患者的病情。

关键词:2 型糖尿病;急性脑梗死;血糖波动;氧化应激;炎症因子

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Type 2 Diabetes Mellitus Complicated with Acute Cerebral Infarction: Effects of Blood Glucose Fluctuation on Oxidative Stress and Inflammatory Factors

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ABSTRACT Objective: To investigate the influence and significance of blood glucose fluctuations on oxidative stress and inflammatory factors in patients with type 2 diabetes mellitus (T2DM) complicated with acute cerebral infarction (ACI). **Methods:** A total of 100 patients with T2DM complicated with ACI, who were treated in Tangdu Hospital of the Fourth Military Medical University from March 2014 to January 2017, were chosen as observation group; and 82 patients with T2DM treated in the hospital in the same period, as control group. The standard deviation of blood glucose (SDBG), daily average blood glucose fluctuation (MAGE), daytime blood glucose fluctuations (MODD), mean amplitude of plasma glucose excursions (MPPGE), malondialdehyde (MDA), urinary 8-iso-prostaglandin F_{2α} (8-iso-PGF_{2α}), tumor necrosis factor-α (TNF-α), high sensitive C reactive protein (hs-CRP) of the two groups were compared. Spearman correlation analysis was used to analyze the correlation between MAGE and MDA, 8-iso-PGF_{2α}, hs-CRP, TNF-α. **Results:** The SDBG, MAGE, MPPGE, MDA, 8-iso-PGF_{2α}, hs-CRP, TNF-α in the observation group were higher than those in the control group, the differences were statistically significant (P<0.05). There was no significant difference in MODD of the two groups (P>0.05). Through the Spearman correlation analysis, MAGE and MDA, 8-iso-PGF_{2α}, hs-CRP, TNF-α were positively related (r=0.657, 0.732, 0.724, 0.538; P=0.013, 0.009, 0.010, 0.021). **Conclusion:** Compared with simple T2DM patients, there is a greater fluctuation of blood glucose in patients with T2DM complicated with ACI, and MAGE is positively related to the levels of oxidative stress and inflammatory factors of the patients. Clinically, the oxidative stress and the levels of inflammatory factors can be reduced by controlling the fluctuation of blood glucose so as to improve the patient's condition.

Key words: Type 2 diabetes mellitus; Acute cerebral infarction; Blood glucose fluctuation; Oxidative stress; Inflammatory factors

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前言

糖尿病是最常见的慢性非传染疾病之一,也是一种以高血糖为主要特征的代谢紊乱疾病,患者不能正常分泌胰岛素或是分泌的胰岛素出现功能缺失,导致体内血糖水平上升^[1,2]。糖尿病可分为1型糖尿病和2型糖尿病(T2DM),其中T2DM最为多见,据流行病学统计,我国是糖尿病患者数量最多的国家,在2007-2008年间,我国成年人的糖尿病人数约有9240万,患病率高达9.7%,而其中有90%以上的属于T2DM,由此可见T2DM已经严重影响我国公民的生活质量,已成为我国一个重要的公共卫生问题^[3,4]。T2DM是急性脑梗死(ACI)的重要危险因素之一,由于持续高血糖会对血管壁造成损伤,导致血管变脆弱,更容易出现破裂和堵塞,增加了ACI的发生率^[5,6]。T2DM合并ACI具有较高的致死率和致残率,同时预后较差,因此研究其相关影响因素,从而采取针对性的预防措施具有重要的意义^[7,8]。相关研究指出,大范围的血糖波动可加重T2DM合并ACI患者的病情^[9,10]。为进一步探讨血糖波动对T2DM合并ACI患者的影响,本研究检测了患者体内氧化应激指标及炎症因子水平,并分析其相关性,现将研究结果报道如下。

1 资料与方法

1.1 一般资料

选取2014年3月到2017年1月第四军医大学唐都医院收治的T2DM合并ACI患者100纳入观察组,纳入标准:①所有患者均确诊为T2DM合并ACI,其中T2DM的诊断标准为《中国2型糖尿病防治指南(2013年版)》^[11]中的相关规定,ACI的诊断标准参考中华医学会神经病学分会脑血管病学组急性缺血性脑卒中诊治指南撰写组制定的《中国急性缺血性脑卒中诊治指南2010》^[12]中的相关规定;②ACI发病到入院时间小于24h;③患者及其家属对本次研究知情同意。排除标准:①1型糖尿病患者;②合并有其他脑部疾病者;③患有恶性肿瘤者;④合并甲状腺功能障碍等其他影响血糖水平的疾病者。观察组男54例,女46例,年龄33-69岁,平均年龄(57.8±9.6)岁,T2DM病程3-12年,平均病程(3.6±1.5)年,体质量指数(BMI)23-27 kg/m²,平均BMI(26.3±3.1)kg/m²。另选取同期在第四军医大学唐都医院接受治疗的单纯T2DM患者82例作为对照组,其中男43例,女39例,年龄31-68岁,平均(56.3±8.9)岁,T2DM病程3-12年,平均(3.8±1.7)年,BMI 23-27 kg/m²,平均BMI

(25.8±3.2)kg/m²。两组患者的性别、年龄、T2DM病程、BMI比较差异不明显(P>0.05),可以进行组间比较。

1.2 测量指标

1.2.1 血糖指标检测 两组患者进行24h血糖监测,仪器选用美国Medtronic MiniMed公司生产的动态血糖监测系统。在患者的腹部皮下处放置具有自动记录功能的埋入式感应探头,通过探头检测葡萄糖浓度,输入血糖值来矫正动态血糖值,4次/d,输入间隔时间小于12h。在监测期间,所有患者的进食时间、进食量、食物种类均无差别。记录24h血糖值后计算以下指标:①血糖水平标准差(SDBG):所有动态血糖值数值的标准差;②日内平均血糖波动幅度(MAGE):血糖波动幅度的均值;③日间血糖波动幅度(MODD):即日间血糖平均绝对差;④平均餐后血糖波动幅度(MPPGE):餐后3h内的血糖峰值与餐前血糖值的平均数。

1.2.2 氧化应激指标和炎症因子的检测 在血糖监测结束后的次日清晨抽取两组患者空腹状况下的静脉血3mL,装入EDTA抗凝管内,离心(3000 r/min,10 min)后取上清液,-80℃的环境下保存待测;收集所有患者的晨尿3mL,-80℃的环境下保存待测。丙二醛(MDA)、尿8-异前列腺素F_{2α}(8-iso-PGF_{2α})、肿瘤坏死因子α(TNF-α)、超敏C反应蛋白(hs-CRP)均采用酶联免疫吸附法进行测定,MDA、TNF-α试剂盒均购自上海普欣生物技术有限公司,8-iso-PGF_{2α}、hs-CRP试剂盒均购自上海拜力生物科技有限公司,所有操作步骤均严格参考试剂盒说明书中的操作指南进行。

1.3 统计学方法

用SPSS19.0进行统计分析,其中计数资料以率(%)的形式表示,采用卡方检验,计量资料以($\bar{x} \pm s$)的形式表示,采用t检验,另外采用Spearman进行相关性分析。以P<0.05为差异有统计学意义。

2 结果

2.1 比较两组患者的血糖指标

观察组的SDBG、MAGE、MPPGE均高于对照组,差异有统计学意义(P<0.05),两组的MODD比较差异无统计学意义(P>0.05),详见表1。

2.2 两组患者的氧化应激指标比较

观察组的MDA、8-iso-PGF_{2α}均高于对照组,差异有统计学意义(P<0.05),详见表2。

表1 两组患者的血糖指标比较(mmL/L)

Table 1 Comparison of blood glucose indexes between two groups (mmol/L)

Groups	n	SDBG	MAGE	MODD	MPPGE
Control group	82	2.05±0.59	4.26±1.58	2.11±0.97	3.68±1.16
Observation group	100	2.48±0.81	5.83±1.75	2.36±0.99	4.51±1.23
t	-	4.012	6.289	1.710	4.647
P	-	0.000	0.000	0.089	0.000

表 2 两组患者的氧化应激指标比较

Table 2 Comparison of oxidative stress indexes between two groups

Groups	n	MDA (mmol/L)	8-iso-PGF _{2α} (mg/mmol)
Control group	82	3.64± 1.24	0.73± 0.32
Observation group	100	5.61± 1.33	1.03± 0.54
t	-	10.248	4.432
P	-	0.000	0.000

2.3 两组的炎症因子的比较

义(P<0.05),详见表3。

观察组的 hs-CRP、TNF-α 均高于对照组,差异有统计学意义

表 3 两组的炎症因子的比较

Table 3 Comparison of inflammatory factors between two groups

Groups	n	hs-CRP (μg/L)	TNF-α (ng/mL)
Control group	82	6.57± 3.89	1.53± 0.43
Observation group	100	9.61± 4.63	1.89± 0.51
t	-	7.431	5.080
P	-	0.000	0.000

2.4 观察组患者 MAGE 与氧化应激指标和炎症因子的相关性

经 Spearman 统计分析, MAGE 与 MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 均呈正相关($r=0.657, 0.732, 0.724, 0.538, P=0.013, 0.009, 0.010, 0.021$)。

3 讨论

T2DM 患者发生 ACI 是导致糖尿病患者死亡、致残的主要原因之一,据相关研究报道, T2DM 患者发生心脑血管疾病的风险是正常人的 2-4 倍,由此可见 T2DM 是 ACI 重要的危险因素, T2DM 患者应注意防范 ACI 的发生^[13,14]。血糖波动是指血糖水平的最高值和最低值之间波动的幅度,正常人也存在一定的血糖波动,但波动幅度普遍较低,多数为无效波动, T2DM 合并 ACI 患者由于机体在短时间内出现巨大变化, 引发了氧化应激反应,导致血糖波动加剧,同时相关研究显示,血糖波动亦可影响氧化应激水平^[15,16]。由此可见,血糖波动和氧化应激反应存在一定的关系。炎症反应是衡量疾病状况的重要指标, ACI 患者由于脑组织缺血、缺氧,导致中性粒细胞炎性浸润,出现炎症反应^[17,18]。

在本次研究中, 观察组的 SDBG、MAGE、MPPGE 均高于对照组, 差异有统计学意义(P<0.05), SDBG、MAGE、MPPGE 均是衡量血糖波动的常用指标, 数值越大代表血糖波动越明显, 这提示 T2DM 合并 ACI 患者的血糖波动幅度要大于单纯 T2DM 患者, 究其原因, T2DM 患者在发生 ACI 后, 由于 ACI 起病急, 机体在很短的时间内出现巨大转变, 进而导致患者出现较为强烈的应激反应, 应激反应促进了肾上腺激素的分泌, 同时也会提升脂肪酸水平和生长激素水平, 促进糖原分解, 导致血糖增高, 另外应激反应也可促进胰高血糖素的分泌, 导致胰岛素受到的对抗更加激烈, 缓解了血糖分解的速度, 变相的导致血糖升高, 因此 T2DM 合并 ACI 患者的血糖波动幅度

会比单纯 T2DM 患者更明显^[19,21]。本研究结果还显示, 观察组的 MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 均高于对照组, 差异有统计学意义(P<0.05)。这提示大幅度的血糖波动的患者其体内氧化应激反应的程度也更高, 且炎症反应也更明显, 血糖波动与氧化应激、炎症反应均有内在联系^[22,23]。究其原因, 氧化应激是指受到刺激后机体大量生成线粒体活性氧簇, 导致抗氧化能力减弱的一种应激状态, MDA、8-iso-PGF_{2α} 均是衡量氧化应激的重要指标, 其数值越大代表氧化应激反应程度越严重^[24,25]。血糖波动幅度过大时易对血管内皮细胞的造成损伤, 同时血糖波动可以激活蛋白激酶 C 通路、多元醇通路、氨基己糖通路等, 导致体内氧化应激反应程度加剧^[26,27]。hs-CRP 是一种由肝细胞合成的急性相蛋白, 当机体受到炎症性刺激时 hs-CRP 的水平变化速度很快, 可以很好的反映炎症程度^[28]。TNF-α 是 ACI 炎症反应中重要的炎症指标, 和凝血、血管内皮损伤均有紧密的联系^[29]。氧化应激反应和炎症反应紧密相关, 由于体内氧化、抗氧化失衡, 中性粒细胞容易产生炎性浸润, 同时蛋白酶分泌增加, 导致白三烯(LT)、血栓素 A2(TXA2)等氧化中间产物大量产生, 其中 LT、TXA2 都是促炎介质, 可加重炎症反应的程度, 由此可见血糖波动越大也可导致炎症反应越剧烈^[30]。MAGE 是衡量血糖波动的金标准, 其变化不仅可以反映血糖的整体水平, 也能体现血糖的离散趋势, 在本研究中, MAGE 与 MDA、8-iso-PGF_{2α}、hs-CRP、TNF-α 均呈正相关(P<0.05), 这说明血糖波动与氧化应激、炎症反应呈正相关, 血糖波动幅度越大, 机体的氧化应激和炎症反应就越严重, 这进一步的证明了三者之间的关系。

综上所述, 与单纯 T2DM 患者相比, T2DM 合并 ACI 患者存在较大的血糖波动, 同时 MAGE 与患者体内的氧化应激及炎症因子水平呈正相关, 临床上可通过控制血糖波动来降低患者的氧化应激反应程度及炎症因子水平, 以改善患者的病情。

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