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· 论 著 ·

2型糖尿病患者一相胰岛素分泌功能特点与糖尿病微血管病变的相关性

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[摘要] **目的** 利用精氨酸刺激试验探讨 2 型糖尿病 (T2DM) 患者一相胰岛素分泌功能特点与糖尿病微血管病变的相关性。**方法** 招募于南通大学附属医院住院治疗的 T2DM 患者 67 例, 其中男 42 例、女 25 例, 年龄为 (56.4±14.2) 岁。根据是否存在微血管病变将患者分为微血管病变组 (病例组, $n=23$) 和无微血管病变组 (对照组, $n=44$)。收集两组患者的身高、体质量、糖尿病病程、肾功能、血脂、尿微量白蛋白与尿肌酐等资料, 计算体质量指数 (BMI)、尿微量白蛋白/肌酐比值 (UACR)、估计的肾小球滤过率 (eGFR)。空腹状态下进行精氨酸刺激试验, 检测空腹和注射精氨酸后 2、4、6 min 血浆葡萄糖水平和血清胰岛素、C 肽水平。计算并比较两组患者的一相胰岛素分泌功能特征, 包括急性胰岛素反应 (AIR) 指数、急性 C 肽反应 (ACR) 指数、胰岛素曲线下面积 (INS_{AUC})、稳态模型评估胰岛素抵抗 (HOMA-IR) 指数等, 并分析其与糖尿病微血管病变的相关性。**结果** 病例组患者的糖尿病病程长于对照组, 差异有统计学意义 ($P=0.030$)。病例组患者的血清肌酐水平, UACR, 空腹和注射精氨酸后 2、4、6 min 胰岛素和 C 肽水平, AIR 指数, INS_{AUC} , HOMA-IR 指数均高于对照组, eGFR 低于对照组, 差异均有统计学意义 (P 均 <0.05)。校正年龄、BMI 后的 logistic 回归分析结果显示, 糖尿病病程、AIR 指数是 T2DM 合并微血管病变的危险因素 [比值比 (OR) = 1.099, 95% 置信区间 (CI): 1.011~1.194, $P=0.026$; $OR=1.049$, 95% CI : 1.007~1.092, $P=0.021$]。**结论** T2DM 微血管病变与糖尿病病程延长、精氨酸刺激后的 AIR 指数升高相关。

[关键词] 2 型糖尿病; 一相胰岛素分泌; 糖尿病血管病变; 糖尿病肾病**[中图分类号]** R 587.1**[文献标志码]** A**[文章编号]** 0258-879X(2018)12-1348-06

Correlation between first-phase insulin secretion and diabetic microvascular complications in patients with type 2 diabetes

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[Abstract] **Objective** To explore the relationship between the first-phase insulin secretion and diabetic microvascular complications in patients with type 2 diabetes mellitus (T2DM) using arginine stimulating test. **Methods** Sixty-seven patients with T2DM, aged (56.4±14.2) years, were enrolled from the Affiliated Hospital of Nantong University, and they included 42 males and 25 females. The patients with microvascular complications were assigned to case group ($n=23$), and the patients without microvascular complications were assigned to control group ($n=44$). The parameters, including height, body mass, duration of diabetes, renal function, plasma lipids, urinary microalbumin, and urine creatinine, were collected. Body mass index (BMI), urinary microalbumin/creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR)

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were calculated. The arginine stimulating test was performed in the fasting state. The levels of plasma glucose, and serum insulin and C-peptide were tested in the fasting state, and at 2, 4 and 6 min after injecting arginine. The acute insulin response (AIR) index, acute C-peptide response (ACR) index, area under curve of insulin (INS_{AUC}) and homeostasis model assessment of insulin resistance (HOMA-IR) index were calculated, and their correlations with diabetic microvascular complications were analyzed. **Results** The duration of diabetes of the T2DM patients in the case group was significantly longer than that in the control group ($P=0.030$). Compared with the control group, the serum creatinine level, UACR, serum insulin and C-peptide levels (in the fasting state and at 2, 4, 6 min after injecting arginine), AIR index, INS_{AUC} , and HOMA-IR index were higher, and the eGFR was lower in the case group, and the differences were significant (all $P<0.05$). The logistic regression analysis after adjusting for age and BMI showed that the duration of diabetes and AIR index were significantly correlated with the diabetic microvascular complications (odds ratio [OR]=1.099, 95% confidence interval [CI] 1.011-1.194, $P=0.026$; OR=1.049, 95% CI 1.007-1.092, $P=0.021$). **Conclusion** The diabetic microvascular complications are associated with the long duration of diabetes and high AIR index in the patients with T2DM.

[Key words] type 2 diabetes mellitus; first-phase insulin secretion; diabetic angiopathies; diabetic nephropathies

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随着经济的快速发展和科技的不断进步, 人们的生产生活方式发生了巨大改变, 2 型糖尿病 (type 2 diabetes mellitus, T2DM) 的发病率也逐年升高^[1], 已成为现代社会致残及致死的危险因素之一。糖尿病微血管病变是糖尿病特有的慢性并发症之一, 主要表现为糖尿病肾病 (diabetic nephropathy, DN)、糖尿病视网膜病变 (diabetic retinopathy, DR) 和糖尿病周围神经病变 (diabetic peripheral neuropathy, DPN), 而持续高血糖是糖尿病微血管病变发生、发展的主要原因之一。一相胰岛素分泌功能异常是导致餐后高血糖和高胰岛素血症的重要环节^[2]。本研究探讨精氨酸刺激后 T2DM 患者一相胰岛素分泌特征及其与 T2DM 微血管病变的相关性, 以期为延缓糖尿病微血管病变的发生、发展提供临床依据。

1 资料和方法

1.1 病例收集与诊断标准 选取 2017 年 10 月至 2018 年 5 月于南通大学附属医院住院治疗的合并 DN 和 DR 的 T2DM 患者 67 例, 其中男 42 例、女 25 例, 年龄为 (56.4±14.2) 岁。具有典型糖尿病症状 (烦渴多饮、多尿、多食、不明原因的体质下降) 并满足以下任一条件即可诊断 T2DM^[3]:

(1) 随机血浆葡萄糖水平 ≥ 11.1 mmol/L (2 g/L); (2) 空腹 (禁食时间 > 8 h) 血浆葡萄糖水平 ≥ 7.0 mmol/L (1.26 g/L); (3) 75 g 葡萄糖负荷后 2 h 血浆葡萄糖水平 ≥ 11.1 mmol/L (2 g/L)。若无典

型糖尿病症状者需改天复查确认。DR 诊断标准^[4]:

所有患者均行免散瞳眼底照相检查初筛、眼底荧光造影确诊, 并且由专业眼科医师复查, 按照 DR 国际临床分级 (2002 年) 的诊断数据进行评估。DN 诊断标准^[5]: 估计的肾小球滤过率 (estimated glomerular filtration rate, eGFR) < 60 mL \cdot min⁻¹ \cdot (1.73 m²)⁻¹ 或 3~6 个月内复查尿微量白蛋白/肌酐比值 (urinary microalbumin/creatinine ratio, UACR) 3 次中至少 2 次尿蛋白排泄增加 (UACR ≥ 30 mg/g)。排除标准:

(1) 1 型糖尿病、妊娠及特殊类型糖尿病; (2) 糖尿病急性并发症; (3) 合并心、肺、肝、肾等器官慢性全身性疾病; (4) 血压控制不佳 [$> 160/100$ mmHg (1 mmHg=0.133 kPa)]; (5) 自身免疫性疾病; (6) 胰腺炎、感染、外伤、手术等应激状态; (7) 皮质醇增多症、甲状腺功能异常等内分泌疾病; (8) 认知障碍等。本研究通过南通大学附属医院伦理委员会审批 (2018-K016)。

1.2 研究设计与分组方法 根据是否存在微血管病变将入组的 T2DM 患者分为 2 组: 微血管病变组 (病例组, $n=23$; T2DM 患者同时合并 DN、DR) 和无微血管病变组 (对照组, $n=44$)。

1.3 观察指标与评估方法 (1) 社会学资料及人体测量学指标: 性别、年龄、身高、体质量、血压、腰围。(2) 精氨酸刺激试验: 取空腹外周静脉血后, 30~60 s 内静脉推注 10% 盐酸精氨酸 (上海信谊金朱药业有限公司) 50 mL (5 g), 注射后 2、4、6 min 抽取外周静脉血测定血浆葡

葡萄糖水平和血清 C 肽、胰岛素水平。(3) 生物化学指标: 血糖、糖化白蛋白 (glycated albumin, GA)、肾功能、血脂、甲状腺功能、血清肌酐等指标由南通大学附属医院生物化学实验室采用德国西门子公司 ADVIA2400 型全自动生化分析仪测定; 采用罗氏 E411 型全自动电化学发光免疫分析仪 (美国罗氏公司) 测定胰岛素、C 肽水平; 采用 BIO-RAD VARIANT™ II 血红蛋白分析仪 (美国 BIO-RAD 公司) 测定糖化血红蛋白 (glycated hemoglobin, HbA_{1c}) 水平; 采用干化学试带法测定尿微量白蛋白水平。(4) 计算公式: 体质量指数 (body mass index, BMI) = 体质量 (kg) / [身高 (m)]²; 急性胰岛素反应 (acute insulin response, AIR) 指数 = (INS₂ + INS₄ + INS₆) / 3 - INS₀, 其中 INS₀、INS₂、INS₄、INS₆ 分别为空腹和注射 10% 盐酸精氨酸后 2、4、6 min 时的胰岛素水平; 急性 C 肽反应 (acute C-peptide response, ACR) 指数 = (CP₂ + CP₄ + CP₆) / 3 - CP₀, 其中 CP₀、CP₂、CP₄、CP₆ 分别为空腹和注射 10% 盐酸精氨酸后 2、4、6 min 时的 C 肽水平; 胰岛素曲线下面积 (area under curve of insulin, INS_{AUC}) = INS₀ + 2INS₂ + 2INS₄ + INS₆; 稳态模型评估胰岛素抵抗 (homeostasis model assessment of insulin resistance, HOMA-IR) 指数 = 空腹血糖 × 空腹胰岛素 / 22.5; eGFR (MDRD) = 186 × (血清肌酐)^{-1.154} × (年龄)^{-0.203} × 0.742 (女性)^[6-9]。

1.4 统计学处理 采用 SPSS 22.0 软件进行数据分析。呈正态分布的计量资料以 $\bar{x} \pm s$ 表示, 两组间比较采用两独立样本 *t* 检验; 呈偏态分布的计量资料以中位数 (下四分位数, 上四分位数) 表示, 两组间比较采用 Mann-Whitney *U* 检验; 计数资料以例数和百分数表示, 组间比较采用 χ^2 检验。以是否合并糖尿病微血管病变为因变量, 年龄、体质量、腰围、糖尿病病程、血脂、HbA_{1c} 水平、GA 水平、AIR 指数、ACR 指数、INS_{AUC} 和 HOMA-IR 指数等为自变量进行 logistic 回归分析。检验水准 (α) 为 0.05。

2 结果

2.1 两组一般资料的比较 病例组患者 23 例, 其中男 17 例、女 6 例, 年龄为 (56.8 ± 11.5)

岁, BMI 为 (25.3 ± 4.4) kg/m², 腰围为 (93.71 ± 13.5) cm; 对照组患者 44 例, 其中男 25 例、女 19 例, 年龄为 (56.2 ± 15.5) 岁, BMI 为 (24.7 ± 4.3) kg/m², 腰围为 (88.4 ± 17.7) cm; 两组性别、年龄、BMI、腰围差异均无统计学意义 (*P* 均 > 0.05)。病例组患者的糖尿病病程长于对照组 [10.0 (5.0, 17.0) 年 vs 3.5 (0.5, 10.0) 年], 差异有统计学意义 (*Z* = -3.787, *P* = 0.030)。病例组患者的血清肌酐水平和 UACR 均高于对照组 [(80.2 ± 21.8) μmol/L vs (55.8 ± 11.0) μmol/L, 15.6 (5.0, 33.9) mg/g vs 2.0 (1.0, 10.5) mg/g], eGFR 低于对照组 [(76.4 ± 18.1) mL · min⁻¹ · (1.73 m²)⁻¹ vs (136.7 ± 25.6) mL · min⁻¹ · (1.73 m²)⁻¹], 差异均有统计学意义 (*t* = -5.046, *Z* = -2.030, *t* = 11.108; *P* 均 < 0.01)。而两组患者的尿酸和血清总胆固醇、三酰甘油、高密度脂蛋白胆固醇、低密度脂蛋白胆固醇、GA、HbA_{1c}、游离三碘甲状腺原氨酸、游离甲状腺素、促甲状腺素水平差异均无统计学意义 (*P* 均 > 0.05)。见表 1。

2.2 两组精氨酸刺激试验相关指标比较 两组患者空腹和注射精氨酸后 2、4、6 min 时血浆葡萄糖水平及 ACR 指数、葡萄糖曲线下面积差异均无统计学意义 (*P* 均 > 0.05)。病例组患者空腹和注射精氨酸后 2、4、6 min 胰岛素和 C 肽水平分别为 7.3 (3.7, 15.8)、33.5 (12.0, 60.3)、22.0 (13.2, 55.9)、15.2 (9.8, 38.2) mU/L 和 2.1 (1.3, 3.2)、3.8 (2.4, 6.2)、2.9 (2.4, 5.2)、2.8 (2.2, 4.6) μg/L, 均高于对照组 [分别为 4.0 (2.1, 5.7)、15.6 (9.2, 21.8)、13.7 (8.2, 20.0)、10.5 (5.4, 15.2) mU/L 和 1.2 (0.9, 2.2)、2.2 (1.5, 3.7)、2.1 (1.6, 3.9)、1.9 (1.4, 3.4) μg/L], 差异均有统计学意义 (*Z* = -2.681、-2.271、-2.641、-2.403 和 -2.456、-2.826、-2.265、-2.357, *P* = 0.007、0.023、0.008、0.016 和 0.014、0.005、0.024、0.018); 病例组患者 AIR 指数、INS_{AUC}、HOMA-IR 指数均高于对照组 [1.2 ± 0.5 vs 0.9 ± 0.3、2.1 ± 0.4 vs 1.9 ± 0.3、3.0 (1.1, 4.9) vs 1.3 (0.7, 2.1)], 差异均有统计学意义 (*t* = -2.417、-2.712, *Z* = -2.272; *P* = 0.018、0.009、0.023)。见表 2。

表 1 两组 T2DM 患者一般资料的比较

Tab 1 Comparison of general characteristics of T2DM patients between two groups

Characteristic	Case group <i>N</i> =23	Control group <i>N</i> =44	Statistic	<i>P</i> value
Male/female <i>n/n</i>	17/6	25/19	$\chi^2=1.887$	0.170
Age (year), $\bar{x}\pm s$	56.8±11.5	56.2±15.5	$t=-0.169$	0.866
Body mass <i>m/kg</i> , $\bar{x}\pm s$	70.4±13.1	68.9±13.6	$t=-0.454$	0.652
BMI ($\text{kg}\cdot\text{m}^{-2}$), $\bar{x}\pm s$	25.3±4.4	24.7±4.3	$t=-0.502$	0.621
Waist circumference <i>l/cm</i> , $\bar{x}\pm s$	93.7±13.5	88.4±17.7	$t=-1.233$	0.222
Duration of diabetes (year), $M(Q_L, Q_U)$	10.0 (5.0, 17.0)	3.5 (0.5, 10.0)	$Z=-3.787$	0.030
SCr $c_B/(\mu\text{mol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	80.2±21.8	55.8±11.0	$t=-5.046$	<0.01
eGFR ($\text{mL}\cdot\text{min}^{-1}\cdot[1.73\text{m}^2]^{-1}$), $\bar{x}\pm s$	76.4±18.1	136.7±25.6	$t=11.108$	<0.01
Uric acid $c_B/(\mu\text{mol}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	267 (242, 325)	296 (241, 381)	$Z=-0.707$	0.598
UACR $w_B/(\text{mg}\cdot\text{g}^{-1})$, $M(Q_L, Q_U)$	15.6 (5.0, 33.9)	2.0 (1.0, 10.5)	$Z=-2.030$	<0.01
TC $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	4.9±1.1	4.8±1.4	$t=-0.163$	0.871
TG $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	1.70 (1.02, 2.77)	1.63 (0.83, 2.39)	$Z=0.417$	0.678
HDL-C $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	1.1±0.3	1.1±0.3	$t=0.260$	0.796
LDL-C $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	2.8±0.9	2.7±0.8	$t=-0.576$	0.566
GA (%), $\bar{x}\pm s$	29.3±8.6	31.4±9.6	$t=-1.000$	0.401
HbA _{1c} (%), $\bar{x}\pm s$	9.9±2.3	9.5±2.2	$t=0.700$	0.464
FT3 $c_B/(\text{pmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	5.1±0.8	4.9±0.6	$t=-1.429$	0.158
FT4 $c_B/(\text{pmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	12.8±2.9	12.3±2.1	$t=-0.795$	0.429
TSH $z_B/(\mu\text{U}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	1.83 (1.07, 3.36)	1.56 (0.99, 2.74)	$Z=-0.660$	0.179

Case group: The patients with microvascular complications; Control group: The patients without microvascular complications. T2DM: Type 2 diabetes mellitus; BMI: Body mass index; SCr: Serum creatinine; eGFR: Estimated glomerular filtration rate; UACR: Urinary microalbumin/creatinine ratio; TC: Total cholesterol; TG: Triglyceride; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; GA: Glycated albumin; HbA_{1c}: Glycated hemoglobin; FT3: Free triiodothyronine; FT4: Free tetraiodothyronine; TSH: Thyroid stimulating hormone; M (Q_L, Q_U): Median (lower quartile, upper quartile)

表 2 两组 T2DM 患者精氨酸刺激试验指标比较

Tab 2 Comparison of arginine stimulation test indexes of T2DM patients between two groups

Index	Case group <i>n</i> =23	Control group <i>n</i> =44	Statistic	<i>P</i> value
PG ₀ $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	8.3±2.2	8.2±2.4	$t=-0.117$	0.905
PG ₂ $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	8.5±2.1	8.5±2.3	$t=-0.128$	0.898
PG ₄ $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	8.9±2.1	8.7±2.4	$t=-0.322$	0.739
PG ₆ $c_B/(\text{mmol}\cdot\text{L}^{-1})$, $\bar{x}\pm s$	9.0±2.1	9.0±2.4	$t=-0.031$	0.976
INS ₀ $z_B/(\text{mU}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	7.3 (3.7, 15.8)	4.0 (2.1, 5.7)	$Z=-2.681$	0.007
INS ₂ $z_B/(\text{mU}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	33.5 (12.0, 60.3)	15.6 (9.2, 21.8)	$Z=-2.271$	0.023
INS ₄ $z_B/(\text{mU}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	22.0 (13.2, 55.9)	13.7 (8.2, 20.0)	$Z=-2.641$	0.008
INS ₆ $z_B/(\text{mU}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	15.2 (9.8, 38.2)	10.5 (5.4, 15.2)	$Z=-2.403$	0.016
CP ₀ $\rho_B/(\mu\text{g}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	2.1 (1.3, 3.2)	1.2 (0.9, 2.2)	$Z=-2.456$	0.014
CP ₂ $\rho_B/(\mu\text{g}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	3.8 (2.4, 6.2)	2.2 (1.5, 3.7)	$Z=-2.826$	0.005
CP ₄ $\rho_B/(\mu\text{g}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	2.9 (2.4, 5.2)	2.1 (1.6, 3.9)	$Z=-2.265$	0.024
CP ₆ $\rho_B/(\mu\text{g}\cdot\text{L}^{-1})$, $M(Q_L, Q_U)$	2.8 (2.2, 4.6)	1.9 (1.4, 3.4)	$Z=-2.357$	0.018
lg (AIR index) $\bar{x}\pm s$	1.2±0.5	0.9±0.3	$t=-2.417$	0.018
ACR index $M(Q_L, Q_U)$	1.2 (0.6, 2.9)	0.9 (0.7, 1.4)	$Z=-1.202$	0.229
GLU _{AUC} $\bar{x}\pm s$	52.3±12.8	50.9±13.5	$t=-0.183$	0.708
lg (INS _{AUC}) $\bar{x}\pm s$	2.1±0.4	1.9±0.3	$t=-2.712$	0.009
HOMA-IR index $M(Q_L, Q_U)$	3.0 (1.1, 4.9)	1.3 (0.7, 2.1)	$Z=-2.272$	0.023

Case group: The patients with microvascular complications; Control group: The patients without microvascular complications. T2DM: Type 2 diabetes mellitus; PG₀, PG₂, PG₄ and PG₆: Plasma glucose levels in the fasting state and at 2, 4 and 6 min after injecting arginine, respectively; INS₀, INS₂, INS₄ and INS₆: Insulin levels in the fasting state and at 2, 4 and 6 min after injecting arginine, respectively; CP₀, CP₂, CP₄ and CP₆: C-peptide levels in the fasting state and at 2, 4 and 6 min after injecting arginine, respectively; AIR: Acute insulin response; ACR: Acute C-peptide response; GLU_{AUC}: Area under curve of glucose; INS_{AUC}: Area under curve of insulin; HOMA-IR: Homeostasis model assessment of insulin resistance; M (Q_L, Q_U): Median (lower quartile, upper quartile)

2.3 T2DM 合并微血管病变影响因素的 logistic 回归分析 以糖尿病微血管病变为因变量,将性别、年龄、体质量、腰围、BMI、糖尿病病程、尿酸水平、血脂、HbA_{1c} 水平、GA 水平、甲状腺功能、AIR 指数、HOMA-IR 指数、葡萄糖曲线下面积、INS_{AUC}、空腹胰岛素和血浆葡萄糖水平作为自变量,采用 logistic 回归模型行多因素分析,以 $P < 0.05$ 为进入标准, $P > 0.10$ 为剔除标准。结果(表3)显示,糖尿病病程、AIR 指数是 T2DM 合并微血管病变的危险因素 (P 均 < 0.05)。

表3 糖尿病微血管病变影响因素的 logistic 回归分析

Tab 3 Logistic regression analysis of influencing factors for diabetic microangiopathy

Variable	B	P value	OR (95% CI)
Duration of diabetes	0.094	0.026	1.099 (1.011, 1.194)
AIR index	0.047	0.021	1.049 (1.007, 1.092)

AIR: Acute insulin response; B: Regression coefficient; OR: Odds ratio; CI: Confidence interval

3 讨论

胰岛素由胰岛素分泌颗粒以胞吐的形式进行释放,分为两相。一相分泌是由释放池的胰岛素分泌颗粒受到刺激(如注射精氨酸)后,无需进一步加工修饰即可释放;二相分泌则是由储备池的胰岛素分泌颗粒通过运动、停泊、融合以及最终的排空过程释放。本研究结果显示,T2DM 合并微血管病变患者的 AIR 指数、INS_{AUC}、HOMA-IR 指数均高于对照组,提示胰岛素抵抗以及代偿性的高胰岛素血症与 T2DM 患者微血管病变的发生有关,这与 Reaven^[10]的研究结论一致。

既往研究证实,T2DM 高胰岛素血症与糖尿病微血管病变有关,甚至在发生显性糖尿病前,即临床糖尿病前期空腹血糖受损和餐后血糖受损阶段,已经出现糖尿病微血管病变^[11]。其机制虽未阐明,但可能与以下几种因素有关:(1)在糖尿病早期阶段,高胰岛素血症可导致氧化应激,从而损伤肾脏及视网膜血管^[12]。(2)在高胰岛素血症刺激下,肝脏脂蛋白合成增加,导致逐渐出现高脂血症^[12]。高胰岛素血症以及高脂血症都可以刺激多种细胞因子释放,促进血管内皮细胞分裂原表达,从而促进视网膜新血管形成 DR^[12-13]。(3)高胰岛素血症可以导致肾脏血流和肾素-血管紧张素-醛固酮系统异常,加重肾小球肥大,损伤肾小球足细

胞^[12,14]。(4)高胰岛素血症引起血管内皮细胞损伤和刺激产生纤溶酶原激活物抑制剂 1,导致血液高凝状态并加重血管疾病^[15]。(5)高胰岛素血症可以激活交感神经系统,促进平滑肌细胞增殖,加重血管伤害^[16]。(6)胰岛素可以显著促进视网膜穆勒细胞的增殖从而导致视网膜病变^[17]。(7)随着胰岛素抵抗和 β 细胞胰岛素分泌增加,胰岛淀粉样多肽也大量释放,导致 β 细胞衰竭和肾小球、肾间质中的淀粉样蛋白沉积^[18];胰岛素还可能通过增加尿酸的重吸收增加患者的尿酸水平,导致高尿酸血症,进一步导致严重的肾损伤^[19]。

有研究显示合并微血管或大血管病变的 T2DM 患者存在胰岛细胞功能减退^[20],与本研究结果并不完全符合。我们推测可能有以下原因:

(1) T2DM 患者在高糖高脂毒性下, β 细胞发生了去分化而非凋亡,这一过程具有一定可逆性,在解除了糖脂毒性后可重新分化为 β 细胞并恢复部分功能^[21]。本研究纳入患者均因高血糖入院,入院后及时予以强化降糖治疗,在胰岛细胞功能有不同程度的恢复后再行精氨酸刺激。由于微血管病变组胰岛素抵抗更严重,出现了代偿性的高胰岛素血症。(2)精氨酸为非糖物质,与生理状态下糖类物质引发的一相分泌有一定差异^[22]。研究显示在胰岛细胞功能减退的情况下,精氨酸仍然能够刺激其产生一相分泌,甚至分泌亢进^[23]。(3)本研究中微血管病变组患者肾功能较对照组减退,肾脏在胰岛素降解过程中也起着不可或缺的作用,微血管病变组一相胰岛素分泌增多是否为降解减少所引起还有待进一步研究证实。

本研究仍有不足之处:(1)糖尿病微血管病变包括 DR、DN、DPN 等,但本研究因条件所限,未进行神经传导速度检测及肾脏活组织检查病理诊断。为增加微血管病变诊断的可靠性,本研究纳入患者为同时具备 DN 和 DR 的临床诊断者。

(2)本研究为横断面研究,仅限于南通地区的人群,且样本量小,只能观察一相分泌功能与微血管并发症的相关性,不能判断二者之间的因果关系,需要进一步前瞻性研究验证。(3)未纳入健康人群作为对照组,故未能观察 T2DM 患者与健康人群一相分泌功能的差异。(4)患者一般资料中,未能采集糖尿病及并发症家族史、用药情况、合并症情况(如大血管病变等)、生长激素或胰岛素样生长因子 1 及微血管病变程度等指标。后续研究将

在进一步扩大样本量的基础上, 增加正常人群及合并 DPN 的患者, 并增加上述指标进行相关分析, 以期获得更精确的结果。

[参 考 文 献]

- [1] International Diabetes Federation. IDF Diabetes Atlas Sixth edition poster update 2014[EB/OL]. [2014-11-10] (2018-08-17). <http://www.idf.org/diabetesatlas/update-2014>.
- [2] OMORI K, NOMOTO H, NAKAMURA A, TAKASE T, CHO KY, ONO K, et al. Reduction in glucose fluctuations in elderly patients with type 2 diabetes using repaglinide: a randomized controlled trial of repaglinide vs sulfonylurea[J/OL]. *J Diabetes Investig*, 2018 Jul 2. doi: 10.1111/jdi.12889.
- [3] MARATHE P H, GAO H X, CLOSE K L. American Diabetes Association standards of medical care in diabetes 2017[J]. *J Diabetes*, 2017, 9: 320-324.
- [4] WILKINSON C P, FERRIS F L 3rd, KLEIN R E, LEE P P, AGARDH C D, DAVIS M, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema disease severity scales[J]. *Ophthalmology*, 2003, 110: 1677-1682.
- [5] ANDRASSY K M. Comments on 'KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease'[J]. *Kidney Int*, 2013, 84: 622-623.
- [6] LEVEY A S, CORESH J, GREENE T, STEVENS L A, ZHANG Y L, HENDRIKSEN S, et al; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate[J]. *Ann Intern Med*, 2006, 145: 247-254.
- [7] SHABIR S, JHAM S, HARPER L, BALL S, BORROWS R, SHARIF A. Validity of glycosylated haemoglobin to diagnose new onset diabetes after transplantation[J]. *Transpl Int*, 2013, 26: 315-321.
- [8] 翟迎九, 周丽诺, 方铭喜, 杨燕萍, 薛莉, 姚蔚. 短期胰岛素强化治疗对新诊断 2 型糖尿病患者相关指标的影响[J]. *中国糖尿病杂志*, 2013, 21: 166-168.
- [9] HAFNER S M, MIETTINEN H, STERN M P. The homeostasis model in the San Antonio Heart Study[J]. *Diabetes Care*, 1997, 20: 1087-1092.
- [10] REAVEN G. Insulin resistance and coronary heart disease in nondiabetic individuals[J]. *Arterioscler Thromb Vasc Biol*, 2012, 32: 1754-1759.
- [11] ABDUL-GHANI M, DEFRONZO R A, JAYYOUSI A. Prediabetes and risk of diabetes and associated complications: impaired fasting glucose versus impaired glucose tolerance: does it matter?[J]. *Curr Opin Clin Nutr Metab Care*, 2016, 19: 394-399.
- [12] ORMAZABAL V, NAIR S, ELFEKY O, AGUAYO C, SALOMON C, ZUÑIGA F A. Association between insulin resistance and the development of cardiovascular disease[J/OL]. *Cardiovasc Diabetol*, 2018, 17: 122. doi: 10.1186/s12933-018-0762-4.
- [13] MUKHERJEE S, GUIDRY C. The insulin-like growth factor system modulates retinal pigment epithelial cell tractional force generation[J]. *Invest Ophthalmol Vis Sci*, 2007, 48: 1892-1899.
- [14] ZHOU M S, SCHULMAN I H, ZENG Q. Link between the renin-angiotensin system and insulin resistance: Implications for cardiovascular disease[J]. *Vasc Med*, 2012, 17: 330-341.
- [15] ZHOU M S, SCHULMAN I H, RAIJ L. Vascular inflammation, insulin resistance, and endothelial dysfunction in salt-sensitive hypertension: role of nuclear factor kappa B activation[J]. *J Hypertens*, 2010, 28: 527-535.
- [16] SHORAKAE S, RANASINHA S, ABELL S, LAMBERT G, LAMBERT E, DE COURTEN B, et al. Inter-related effects of insulin resistance, hyperandrogenism, sympathetic dysfunction and chronic inflammation in PCOS[J]. *Clin Endocrinol (Oxf)*, 2018, 89: 628-633.
- [17] 孙伟英, 张晓梅, 郑玲. 胰岛素对视网膜 Müller 细胞生长活力的影响[J]. *中国伤残医学*, 2008, 16: 10-12.
- [18] CHEN Y C, TAYLOR A J, VERCHERE C B. Islet prohormone processing in health and disease[J]. *Diabetes Obes Metab*, 2018, 20(Suppl 2): 64-76.
- [19] TSUNODA S, KAMIDE K, MINAMI J, KAWANO Y. Decreases in serum uric acid by amelioration of insulin resistance in overweight hypertensive patients: effect of a low-energy diet and an insulin-sensitizing agent[J]. *Am J Hypertens*, 2002, 15: 697-701.
- [20] MULVEY C, MCNEILL A M, GIRMAN C J, CHURCHILL T W, TEREMBULA K, FERGUSON J F, et al. Differential associations of oral glucose tolerance test-derived measures of insulin sensitivity and pancreatic β -cell function with coronary artery calcification and microalbuminuria in type 2 diabetes[J]. *Diabetes Care*, 2014, 37: 124-133.
- [21] TALCHAI C, XUAN S, LIN H V, SUSSEL L, ACCILI D. Pancreatic β cell dedifferentiation as a mechanism of diabetic β cell failure[J]. *Cell*, 2012, 150: 1223-1234.
- [22] RYAN E A, LAKEY J R, PATY B W, IMES S, KORBUTT G S, KNETEMAN N M, et al. Successful islet transplantation: continued insulin reserve provides long-term glycemic control[J]. *Diabetes*, 2002, 51: 2148-2157.
- [23] BLACHIER F, MOURTADA A, SENER A, MALAISSE W J. Stimulus-secretion coupling of arginine-induced insulin release. Uptake of metabolized and nonmetabolized cationic amino acids by pancreatic islets[J]. *Endocrinology*, 1989, 124: 134-141.