·临床研究·

2 型糖尿病患者糖化血红蛋白水平与内皮功能评估指数的相关性

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【摘 要】 **目的** 探讨糖化血红蛋白(HbA1c)与反应性充血指数(RHI)的相关性。**方法** 入选 2017 年 1 月至 2019 年 2 月南京医科大学第一附属医院内分泌科收治的 2 型糖尿病患者 608 例,住院期间所有患者均使用 Endo-PAT 无创血管内皮功能检测技术计算出评估指数 RHI。根据 RHI 结果分组,RHI≥1.67 为对照组,RHI<1.67 为观察组;根据 HbA1c 水平分为 HbA1c<7%组、HbA1c 7%~9%组和 HbA1c>9%组。比较各组的一般资料、生化指标、血糖及胰岛素抵抗指标等。采用 Spearman 相关性分析评估 HbA1c 与 RHI 相关性;采用多元线性回归分析影响内皮功能的因素,评估 HbA1c 与 RHI 的关系。**结果** 与对照组相比,观察组 HbA1c 明显增高($P=0.001$),而年龄、体质量指数、血脂、血糖、稳态模型胰岛素抵抗指数、稳态模型胰岛 β 细胞功能指数等无统计学意义($P>0.05$)。不同 HbA1c 亚组间随 HbA1c 水平升高 RHI 降低($P=0.004$)。Spearman 相关分析提示 2 型糖尿病患者 HbA1c 与 RHI 呈明显负相关,多因素回归和 logistic 回归分析显示 HbA1c 是血管内皮功能评估指数的独立显著预测因子($OR=0.864$,95%CI 0.786~0.950,$P=0.002$)。**结论** 对于 2 型糖尿病患者,通过检测 HbA1c 可以评估近期内皮功能情况;通过积极控制血糖水平,可改善其血管内皮功能障碍,从而降低周围血管等靶器官损害和预防心血管事件。

【关键词】 糖尿病,2 型;糖化血红蛋白;内皮功能;反应性充血指数

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Relationship between glycosylated hemoglobin A1c and vascular endothelial function assessment hyperemia index in patients with type 2 diabetes mellitus

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【**Abstract**】 **Objective** To investigate the correlation between glycosylated hemoglobin A1c (HbA1c) and reactive hyperemia index (RHI) in the patients with type 2 diabetes mellitus (T2DM). **Methods** A total of 608 T2DM patients admitted to the Endocrinology Department of First Affiliated Hospital of Nanjing Medical University from January 2017 to February 2019 were enrolled in this study. During the hospitalization, all patients were evaluated by using Endo-PAT non-invasive vascular endothelial function detection technology to calculate RHI. The patients with RHI≥1.67 were assigned into the control group, and those with RHI<1.67 were into the study group. According to the HbA1c level, they were divided into HbA1c <7% group, HbA1c 7%-9% group and HbA1c >9% group. Their general data, biochemical indices, blood glucose level and insulin resistance index were compared among the groups. Spearman correlation analysis was used to evaluate the correlation between HbA1c and RHI. The relationship was evaluated by multiple linear regression analysis on the factors affecting endothelial function. **Results** HbA1c level was significantly higher in the study group than in the control group ($P=0.001$), but no statistical significances were seen in age, body mass index, blood lipid, blood glucose, and homeostatic model assessment of insulin resistance (HOMA-IR) and of β-cell function (HOMA-β) between two groups. With the increase of HbA1c, RHI was decreased in the groups of different HbA1c level ($P=0.004$). Spearman correlation analysis showed that HbA1c level was negatively correlated with RHI in T2DM patients, and multivariate regression and logistic regression analysis indicated that HbA1c was an independent and significant predictor for vascular endothelial function assessment index ($OR=0.864$, 95%CI 0.786-0.950, $P=0.002$). **Conclusion** For T2DM patients, HbA1c can be used to evaluate the recent endothelial function. Actively controlling the blood glucose can improve vascular endothelial dysfunction, and thus the damage to peripheral vessels and other target organs will be thereby reduced and cardiovascular events be prevented.

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【Key words】 diabetes mellitus, type 2; glycosylated hemoglobin A1c; endothelial function; reactive hyperemia index
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糖尿病是一种常见的慢性代谢疾病,其患病率的上升是全球性的公共卫生问题[1]。其引发的各种并发症,例如视网膜病、肾病、糖尿病足和血管疾病带来了巨大的社会经济负担。作为糖尿病最严重的表现之一,心血管并发症是糖尿病致死和致残的主要原因。尽管糖尿病引起心血管疾病的潜在机制是多因素的和复杂的,但血管内皮功能障碍起着重要作用[2]。内皮功能障碍是动脉粥样硬化的始动环节,并全程参与动脉粥样硬化的进程,在心血管事件中起重要作用[3]。因此,预测糖尿病患者内皮功能情况、并进行及时有效的临床干预具有重要的意义。反应性充血外周动脉张力测定法(reactive hyperemia peripheral arterial tonometry, RH-PAT)是目前非侵入性检测内皮功能的最新手段,具有无创、自动和定量特点[4],其计算出的反应性充血指数(reactive hyperemia index, RHI)是近年来用于临床评估血管内皮功能和动脉粥样硬化的有效指标,但目前在国内属于起步阶段,尚未普及。Framingham心脏研究报告指出,RHI与多种传统和代谢性心血管危险因素负相关[5]。多个临床前瞻性试验证明了RH-PAT可显著预测心血管事件,RHI评估的外周内皮功能是预测未来心血管事件的重要指标[6]。糖化血红蛋白(glycosylated hemoglobin Alc, HbA1c)作为血糖控制的主要标志物,主要反映患者近2~3个月的血糖平均水平,已经成为国际上普遍公认的反映糖尿病长期血糖监控的金标准[7]。HbA1c在血液中检测结果稳定,操作方便,患者依从性高。因此,本研究探索2型糖尿病(type 2 diabetes mellitus, T2DM)患者HbA1c和血管内皮功能指标RHI的相关性,以便在慢性糖尿病病程中通过定期HbA1c监测早期发现内皮功能损伤,早期干预,预防心脑血管并发症发生。

1 对象与方法

1.1 研究对象

入选2017年1月至2019年2月南京医科大学第一附属医院内分泌科收治的T2DM患者608例,其中男性387例,女性221例,年龄18~87岁。诊断标准依据《中国2型糖尿病防治指南(2017年版)》。排除标准:(1)继发性糖尿病、1型糖尿病;(2)酮症酸中毒、高血糖高渗状态;(3)严重心、脑血管意外;(4)并发严重肝肾衰竭、感染性疾病等其他严重器质性疾病;(5)长期服用糖皮质激素,合并精神疾病;(6)不配合治疗措施;(7)妊娠期妇女。住院期间所有患者均使用RH-PAT检测RHI。以RHI<1.67作为血管内皮功能受损的评估标准[8],RHI≥1.67患者227例为对照组,RHI<1.67患者381为观察组例。《中国2型糖尿病防治指南(2017年)》指出,对大多数非妊娠成年T2DM患者而言,合理的HbA1c控制目标为<7.0%;并有研究证实当HbA1c>9.0%时,心血管疾病的发病率增加[9]。据此,将患者分为3组:HbA1c<7%组121例、HbA1c 7%~9%组253例和HbA1c>9%组234例。

1.2 方法

1.2.1 临床资料 所有纳入者均由内分泌专科医师接诊询问病史,采集性别、年龄,并进行体格检查,测量身高、体质量、收缩压(systolic blood pressure, SBP)和舒张压(diastolic blood pressure, DBP)。

1.2.2 实验室检测 所有纳入者在空腹10~12 h后于次日清晨抽取肘静脉血,分别检测谷氨酸氨基转移酶(alanine transaminase, ALT)、天冬氨酸氨基转移酶(aspartate transaminase, AST)、总胆固醇(total cholesterol, TC)、甘油三酯(triglycerides, TG)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、肌酐(creatinine, Cr)、尿酸(uric acid, UA)、空腹血糖(fasting blood glucose, FPG)、空腹胰岛素(fasting insulin, FINS)、HbA1c等。采用BECKMAN-AU5800全自动生化分析仪检测生化指标,高效液相色谱法检测HbA1c(美国伯乐),化学发光法检测FINS。上述指标均由本院检验科专业人士完成检测,所有检测过程都严格按照标准操作流程进行。

1.2.3 微血管内皮功能的检测方法 采用无创外周动脉张力测定(peripheral arterial tonometry, PAT)法进行微血管内皮功能的评估(Endo-PAT2000, Itamer医疗有限公司,凯撒利亚,以色列),通过在双手食指放置1个PAT指套及脉冲振幅的形式记录不同时间指尖动脉的血容量体积的改变。该检测方法主要包括3个阶段:(1)基线数据的测量;(2)血流阻断时的测量;(3)反应性的充血期。检测结束后,计算机系统根据其检测期间的数据收集计算出

相应的结果,其中 RHI 用于评估微血管的内皮功能。我中心将 RHI<1.67 作为血管内皮功能受损的评估指标。RHI 越小,表示血管内皮功能障碍越重。

1.2.4 胰岛β细胞功能相关标准 (1)稳态模型胰岛素抵抗指数(homeostasis model assessment of insulin resistance, HOMA-IR)。HOMA-IR = (FBG × FINS)/22.5。(2)稳态模型胰岛β细胞功能指数(homeostasis model assessment of β cell function, HOMA-β)。HOMA-β=20 × FINS/(FBG−3.5)。

1.3 统计学处理

采用 SPSS 24.0 统计软件进行分析。计量资料呈正态分布者以均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本 t 检验,不符合正态分布者以中位数和四分位数间距[$M(Q_1,Q_3)$]表示,组间比较采用 Mann-Whitney U 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。多组间比较采用单因素方差分析或者 Kruskal-Wallis H 检验。采用 Spearman 非参数相关分析 HbA1c 水平与 RHI 之间的关系。对有相关性的因子进一步采用多元线性 logistic 回归分析2型糖尿病患者内皮功能障碍的危险因素。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2组患者基线资料比较

2组患者性别、年龄、血压、肝肾功能及血脂比较,差异均无统计学意义(均 $P>0.05$)。RHI<1.67 观察组 HbA1c 水平高于 RHI≥1.67 对照组,差异有统计学意义($P<0.05$;表1)。

2.2 不同 HbA1c 水平亚组临床指标比较

纳入的 T2DM 患者根据 HbA1c 水平分为3组:HbA1c<7% 组、HbA1c 7%~9%组、HbA1c >9%组,随着 HbA1c 水平增加,血管内皮功能评估指数 RHI 值、FINS、HOMA-β 和 HOMA-IR 降低,而 FPG 升高,差异均有统计学意义(均 $P<0.05$;表2)。

2.3 T2DM 患者 HbA1c 水平和内皮功能指标 RHI 的相关性分析

将 T2DM 患者的 RHI 与一般临床资料进行 Spearman 相关性分析,结果显示年龄和 HbA1c 水平与 RHI 呈负相关($P<0.05$)。同时,患者血压、BMI、TC、TG、HDL-C、LDL-C、AST、ALT、Cr、UA、FPG、FINS、HOMA-β 和 HOMA-IR 均与 RHI 无相关性($P>0.05$;表3)。

表1 2组患者一般资料及生化指标比较

Table 1 Comparison of baseline data between two groups

Item	RHI < 1.67 group (n=381)	RHI ≥ 1.67 group (n=227)	$\chi^2/t/z$	P value
Gender(male/female, n)	231/150	156/71	4.026	0.050
Age(years, $\bar{x}\pm s$)	60.36±12.70	59.04±12.29	1.261	0.208
BMI(kg/m^2, $\bar{x}\pm s$)	25.43±3.36	25.29±3.17	0.488	0.626
SBP(mmHg, $\bar{x}\pm s$)	134.23±17.64	135.83±19.41	−1.043	0.297
DBP(mmHg, $\bar{x}\pm s$)	77.43±11.75	78.90±12.56	−1.450	0.148
AST[U/L, $M(Q_1, Q_3)$]	20.10(16.55, 24.60)	20.40(16.90, 24.90)	−0.831	0.406
ALT[U/L, $M(Q_1, Q_3)$]	20.50(14.00, 29.10)	19.20(14.30, 30.10)	−0.205	0.837
FPG[mmol/L, $M(Q_1, Q_3)$]	7.08(5.90, 8.24)	6.97(5.88, 7.78)	−1.213	0.225
FINS[μU/ml, $M(Q_1, Q_3)$]	6.19(3.17, 11.50)	6.19(3.53, 10.54)	−0.193	0.847
HDL-C[mmol/L, $M(Q_1, Q_3)$]	1.02(0.88, 1.17)	1.02(0.88, 1.21)	−0.697	0.486
LDL-C[mmol/L, $M(Q_1, Q_3)$]	2.98(2.40, 3.62)	2.87(2.27, 3.41)	−1.330	0.184
TG[mmol/L, $M(Q_1, Q_3)$]	1.37(0.98, 2.13)	1.33(0.87, 2.03)	−1.169	0.242
TC[mmol/L, $M(Q_1, Q_3)$]	4.62(3.80, 5.48)	4.44(3.67, 5.26)	−1.431	0.152
Cr[μmol/L, $M(Q_1, Q_3)$]	65.30(55.00, 76.00)	65.40(56.70, 78.40)	−1.306	0.191
UA[μmol/L, $M(Q_1, Q_3)$]	320.60(265.95, 383.00)	325.00(272.00, 392.00)	−0.631	0.528
HOMA-β[$M(Q_1, Q_3)$]	35.33(18.24, 72.21)	38.82(21.02, 71.50)	−0.675	0.499
HOMA-IR[$M(Q_1, Q_3)$]	1.93(0.90, 3.94)	1.92(0.97, 3.51)	−0.056	0.956
HbA1c[%, $M(Q_1, Q_3)$]	8.70(7.30, 10.15)	7.90(7.00, 9.40)	−3.437	0.001

RHI: reactive hyperemia index; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase; FPG: fasting plasma glucose; FINS: fasting insulin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; TC: total cholesterol; Cr: creatinine; UA: uric acid; HOMA-β: homeostasis model assessment of β cell function; HOMA-IR: homeostasis model assessment of insulin resistance; HbA1c: glycosylated hemoglobin A1c. 1 mmHg=0.133 kPa.

表2 不同HbA1c水平亚组临床指标的比较

Table 2 Comparison of clinical indices among different subgroups of HbA1c level

Item	HbA1c<7% group (n=121)	HbA1c 7%-9% group (n=253)	HbA1c>9% group (n=234)	χ^2/H	P value
Gender(male/female, n)	77/44	151/102	159/75	3.589	0.166
Age[years, $M(Q_1, Q_3)$]	61.00(54.50, 66.00)	61.00(53.00, 67.50)	61.00(52.00, 68.00)	0.493	0.782
BMI[kg/m^2, $M(Q_1, Q_3)$]	24.82(22.95, 26.48)	25.10(23.33, 27.29)	25.00(23.17, 27.45)	2.017	0.365
SBP[mmHg, $M(Q_1, Q_3)$]	131.00(120.50, 144.50)	135.00(124.50, 145.50)	134.50(122.00, 147.00)	2.458	0.293
DBP[mmHg, $M(Q_1, Q_3)$]	77.00(70.00, 85.00)	77.00(69.00, 84.50)	78.50(70.00, 88.00)	5.372	0.068
AST[U/L, $M(Q_1, Q_3)$]	19.90(16.90, 24.45)	20.80(17.20, 24.80)	19.80(15.88, 24.83)	4.332	0.115
ALT[U/L, $M(Q_1, Q_3)$]	17.80(13.15, 27.60)	20.70(14.85, 31.40)	20.55(13.58, 28.90)	5.680	0.058
FPG[mmol/L,$M(Q_1, Q_3)$]	6.32(5.50, 7.12)	7.12(6.03, 8.01)	7.32(6.07, 8.45)	34.633	<0.001
FINS[μU/ml,$M(Q_1, Q_3)$]	8.21(4.77, 13.23)	6.87(3.81, 12.56)	4.45(2.27, 9.22)	31.485	<0.001
HDL-C[mmol/L,$M(Q_1, Q_3)$]	1.06(0.92, 1.20)	1.04(0.88, 1.21)	0.98(0.87, 1.14)	7.768	0.021
LDL-C[mmol/L,$M(Q_1, Q_3)$]	2.77(2.16, 3.43)	2.97(2.25, 3.51)	2.99(2.45, 3.72)	6.146	0.046
TG[mmol/L,$M(Q_1, Q_3)$]	1.28(0.87, 1.86)	1.37(1.00, 2.15)	1.37(0.95, 2.29)	4.321	0.115
TC[mmol/L,$M(Q_1, Q_3)$]	4.37(3.49, 5.16)	4.56(3.67, 5.35)	4.63(3.95, 5.63)	6.573	0.037
Cr[μmol/L, $M(Q_1, Q_3)$]	63.90(56.65, 78.10)	66.90(56.75, 76.75)	64.70(53.55, 76.33)	2.371	0.306
UA[μmol/L, $M(Q_1, Q_3)$]	352.00(301.50, 405.75)	313.80(263.00, 379.00)	319.50(261.93, 374.80)	10.526	0.005
HOMA-β[$M(Q_1, Q_3)$]	62.49(35.83, 93.91)	41.45(22.80, 69.20)	23.35(14.24, 52.27)	66.152	<0.001
HOMA-IR[$M(Q_1, Q_3)$]	2.46(1.26, 3.72)	2.20(1.11, 4.27)	1.57(0.70, 3.01)	19.863	<0.001
RHI[$M(Q_1, Q_3)$]	1.59(1.35, 1.95)	1.58(1.41, 1.88)	1.51(1.30, 1.73)	10.887	0.004

HbA1c: glycosylated hemoglobin A1c; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase; FPG: fasting plasma glucose; FINS: fasting insulin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglycerides; TC: total cholesterol; Cr: creatinine; UA: uric acid; HOMA-β: homeostasis model assessment of β cell function; HOMA-IR: homeostasis model assessment of insulin resistance; RHI: reactive hyperemia index. 1 mmHg=0.133 kPa.

表3 RHI与各指标相关性分析

Table 3 Correlation analysis between RHI and each index

Index	RHI	
	r	P value
Age	−0.116	0.004
BMI	−0.024	0.556
SBP	0.049	0.230
DBP	0.079	0.050
AST	0.047	0.252
ALT	0.054	0.184
FPG	−0.037	0.359
FINS	0.008	0.850
LDL-C	−0.006	0.890
HDL-C	0.053	0.195
TC	−0.011	0.779
TG	−0.047	0.247
Cr	0.012	0.777
UA	−0.001	0.983
HbA1c	−0.144	<0.001
HOMA-β	0.032	0.436
HOMA-IR	0.001	0.980

RHI: reactive hyperemia index; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; AST: aspartate transaminase; ALT: alanine transaminase; FPG: fasting plasma glucose; FINS: fasting insulin; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; Cr: creatinine; UA: uric acid; HbA1c: glycosylated hemoglobin A1c; HOMA-β: homeostasis model assessment of β cell function; HOMA-IR: homeostasis model assessment of insulin resistance. 1 mmHg=0.133 kPa.

2.4 影响内皮功能的多因素线性回归分析和logistic回归分析

将单因素分析中有统计学差异的因素和既往内皮功能研究中有相关性的指标进行回归分析，以RHI为因变量，在校正年龄、BMI、空腹血糖、血脂、血压等变量影响后，进行多因素线性回归分析，结果提示T2DM患者内皮功能障碍主要受HbA1c水平影响(P<0.05；表4)。并以上述的指标为自变量，以是否出现内皮功能障碍为因变量，logistic回归分析显示，HbA1c仍是T2DM患者发生内皮功能障碍独立危险因素(表5)。

3 讨 论

糖尿病是一种代谢性疾病，其特征在于胰岛素分泌和(或)胰岛素作用缺陷引起的高血糖，且长期高血糖会引起大血管和微血管并发症，而内皮功能障碍在这些并发症的发生和发展中起着重要病理生理作用[10]。内皮功能障碍是动脉硬化的始动环节，并参与炎症和血栓形成[11,12]。Endo-PAT无创血管内皮功能诊断系统是唯一通过美国食品药品监督管理局认证的内皮功能无创诊断设备。通过检测计算RHI，能够精确量化血管内皮功能状态，是心血管事件的理想预测因子之一[13]。血管内皮功能障碍的主要表现是血管内皮细胞依赖性舒张功能受损，主

表4 RHI影响因素的多元线性回归分析

Table 4 Multiple linear regression analysis of the influencing factors of RHI

Variable	Unstandardized coefficient		Standardized coefficient	t	P value
	β	SE	β		
Age	−0.006	0.002	−0.165	−3.450	0.001
BMI	−0.010	0.005	−0.080	−1.885	0.060
SBP	0.001	0.001	0.030	0.589	0.556
DBP	0.001	0.002	0.035	0.664	0.507
HbA1c	−0.028	0.009	−0.131	−3.137	0.002
FINS	0.000	0.000	−0.018	−0.453	0.650
FPG	0.006	0.011	0.023	0.538	0.591
TC	−0.051	0.083	−0.155	−0.618	0.537
TG	0.007	0.020	0.030	0.341	0.733
HDL-C	0.170	0.110	0.106	1.540	0.124
LDL-C	0.031	0.099	0.067	0.307	0.759

RHI: reactive hyperemia index; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated hemoglobin A1c; FINS: fasting insulin; FPG: fasting plasma glucose; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

要是一氧化氮(nitric oxide, NO)生物利用度下降[14]。而PAT技术测量正是利用NO介导的血管反应反映内皮功能[15]。

HbA1c即非酶促的血红蛋白的糖基化反应产物,由血糖和血红蛋白的结合生成,是不可逆反应,并与血糖浓度成正比,与红细胞的寿命大体一致,能够反映过去2~3个月血糖控制的平均水平,它不受偶尔一次血糖升高或降低的影响,因此,对HbA1c进行测定,可以比较全面地了解过去一段时间的血糖控制水平。空腹血糖、餐后血糖以及OGTT试验只能反映某一具体时间的血糖水平,并容易受到进食和糖代谢等相关因素的影响,而HbA1c不受抽血时间、是否空腹以及使用胰岛素等因素干扰。早有前瞻性研究发现HbA1c与长期糖尿病并发症的风险相关,HbA1c每降低1%,微血管并发症风险降低37%,与糖尿病相关的任何终点或死亡风险降低21%[16]。本研究中RHI观察组HbA1c明显高于对照组,同时HbA1c分组中随着HbA1c升高,RHI水平明显降低,说明随着HbA1c浓度的增加,血管的内皮依赖性舒张功能随之下降,反映出HbA1c升高与血管内皮细胞损伤相关。在二者相关性分析中,HbA1c水平与RHI呈显著正相关。既往研究中,衰老、肥胖、高血压和糖尿病是导致血管硬化恶化改变的公认因素,故本研究使用年龄、BMI、血脂、血压、血糖和HbA1c水平对血管内皮功能指标RHI进行多因素线性回归分析和logistic回归分析,结果显示HbA1c水平是糖尿病患者血管内皮功能独立危险因素。故对于糖尿病患者,长期平均血糖水平是影响内皮功能的主要因素。尽管糖尿病可通过多种机制损伤血管,但推测HbA1c水平与内皮功能障碍的关联性主要归因于长期高血糖状态下使血红蛋白容易发生糖基化,并且容易形成晚期糖基化终末产物(advanced glycation end products, AGEs)。AGEs的形成与血管内皮损伤的发生密切相关。首先,最主要的机制是诱导产生活性氧引起氧化应激,使NO失活,从而通过降低NO生物利用度而触发内皮依赖性舒张功能受损[17]。其次,AGEs可能通过减少前列环素、增加内皮素1的表达,破坏内皮细胞平衡[18]。最后,随着血红蛋白的糖基化加重,其携氧能力下降,释放氧能力也下降,引起血管内皮细胞缺血、缺氧及损伤。

随着年龄的增加,血管内皮功能也逐渐下降,动脉硬化的发生成为必然,本研究也发现RHI和年龄

表5 多因素logistic回归分析相关参数

Table 5 Multivariate logistic regression analysis of related parameters

Variable	B	SE	$Wald$	OR	95%CI	P value
HbA1c	−0.148	0.048	10	0.862	0.785−0.947	0.002
Age	−0.014	0.008	3	0.986	0.970−1.002	0.089
BMI	−0.024	0.028	1	0.976	0.924−1.031	0.379
FINS	0.000	0.002	0	1.000	0.996−1.003	0.951
FPG	−0.014	0.056	0	0.986	0.883−1.101	0.799
SBP	0.006	0.006	1	1.006	0.994−1.017	0.338
DBP	0.008	0.009	1	1.008	0.990−1.026	0.394
TC	0.186	0.426	0	1.205	0.522−2.779	0.662
TG	−0.076	0.102	1	0.927	0.759−1.133	0.459
HDL-C	0.177	0.558	0	1.194	0.400−3.562	0.751
LDL-C	−0.388	0.511	1	0.679	0.249−1.847	0.448

RHI: reactive hyperemia index; BMI: body mass index; FINS: fasting insulin; FPG: fasting plasma glucose; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglycerides; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

呈负相关,表明随着年龄增加,检测 RHI 逐渐降低。校正各种影响因素后,升高的 HbA1c 水平仍然是内皮功能的独立危险因素,对预测冠状动脉粥样硬化有一定的价值。本研究结果还提示:传统的心血管危险因素如 BMI、SBP、TG、TC、LDL-C 等都与糖尿病患者内皮功能障碍无明显相关性。我们分析与研究人群有关,本研究是血糖控制不佳入院治疗的糖尿病患者,往往内皮功能已经受损,这些传统危险因素与长期高血糖对患者内皮功能影响比较可能相对较小。另外本研究纳入患者未采集近期改善血管内皮功能的用药情况,这也是本研究的不足之处。尚需进一步细化研究验证,并对患者进行长期随访,可在后续研究中深入探索。

综上,本研究发现 T2DM 患者中 HbA1c 水平对内皮功能障碍存在预测价值,对 T2DM 的风险分层有帮助;同时评价内皮功能可确定糖尿病患者是否需要尽早开始改善血管内皮功能的药物治疗。由于糖尿病与内皮功能障碍的关系密切,有研究甚至提示微血管损伤可能先于糖尿病的表现,并有证据表明内皮功能障碍不仅可能是 T2DM 的后果,而且可能是其发生的先兆,甚至可以预测 T2DM 的发生[19]。内皮功能在动脉粥样硬化从开始到动脉粥样硬化血栓形成的各个阶段都起着关键作用,并且在每个阶段都是可逆的,这表明内皮功能导向治疗的实用性[13]。如多项研究中发现他汀类药物可改善内皮细胞功能[20],早期干预能降低心血管事件的风险。因此,糖尿病患者应定期常规检测 HbA1c,不仅是糖尿病诊断和血糖水平控制的重要标志物,也是评估血管并发症及疗效观察的基石,临床可以对糖尿病患者进行适时干预,通过控制 HbA1c 的水平预防心血管疾病的发生。

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