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HbA1c、LDL-C 与 2 型糖尿病下肢动脉血管病变的相关性

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[摘要] 目的: 探讨糖化血红蛋白(glycosylated hemoglobin, HbA1c)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)与2型糖尿病(type 2 diabetes mellitus, T2DM)患者下肢动脉血管病变(lower extremity arterial disease, LEAD)的相关性。方法: 选取2018年5月至2021年5月华东师范大学附属芜湖医院收治的T2DM患者96例, 根据双下肢彩超是否有斑块将患者分为单纯T2DM组($n=47$)与T2DM合并LEAD组($n=49$)。比较两组血清HbA1c、LDL-C等指标差异, 对HbA1c、LDL-C水平与双下肢血管病变的相关性进行多元逐步回归分析, 采用受试者工作特征(receiver operating characteristic, ROC)曲线评价HbA1c、LDL-C对LEAD的诊断能力。结果: 两组空腹血糖、HbA1c、总胆固醇、三酰甘油、LDL-C水平差异均有统计学意义($t=-3.345$ 、 5.022 、 -2.721 、 -2.494 、 2.462 , 均 $P<0.05$)。多元逐步回归分析显示: 血清HbA1c、LDL-C水平与T2DM患者发生LEAD相关($t=-3.823$ 、 -2.493 , $P<0.05$)。ROC曲线分析显示: HbA1c的ROC曲线下面积为0.680, 诊断LEAD的敏感度为60.0%, 特异度为70.6%; LDL-C的ROC曲线下面积为0.727, 敏感度为61.2%, 特异度为76.5%。结论: T2DM合并LEAD患者血清HbA1c、LDL-C水平显著增高, HbA1c、LDL-C有望作为LEAD的诊断指标。

[关键词] 下肢动脉病变; 2型糖尿病; 糖化血红蛋白; 低密度脂蛋白胆固醇

Correlation between HbA1c, LDL-C and lower extremity arterial disease in type 2 diabetes mellitus

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Abstract **Objective:** To investigate the correlation between glycosylated hemoglobin (HbA1c), low-density lipoprotein cholesterol (LDL-C) and lower extremity arterial disease (LEAD) in patients with type 2 diabetes mellitus (T2DM). **Methods:** A total of 96 patients with T2DM admitted to our hospital from May 2018 to May 2021 were selected. The patients were divided into a T2DM alone group ($n=47$) and a T2DM combined with LEAD group ($n=49$) according to whether there were plaques in the lower limbs. The differences in

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serum HbA1c and LDL-C and other indicators were compared between the two groups. The correlation between HbA1c and LDL-C levels and vascular lesions of both lower extremities was analyzed by multiple stepwise regression analysis. The diagnostic ability of HbA1c and LDL-C for LEAD was evaluated by receiver operating characteristic (ROC) curve. **Results:** The differences of fasting plasma glucose, HbA1c, total cholesterol, triglyceride, LDL-C levels and the proportion of hypertension between the 2 groups were statistically significant ($t=-3.345, 5.022, -2.721, -2.494, 2.462$, all $P<0.05$). Multiple stepwise regression analysis showed that serum HbA1c and LDL-C levels were correlated with LEAD in T2DM patients ($t=-3.823, -2.493$, $P<0.05$). The area under ROC curve of HbA1c was 0.680, and the sensitivity and specificity of LEAD were 60.0% and 70.6%, respectively. The area under ROC curve of LDL-C was 0.727, the sensitivity was 61.2%, and the specificity was 76.5%. **Conclusion:** The serum levels of HbA1c and LDL-C in T2DM patients with LEAD are significantly increased, and HbA1c and LDL-C are expected to be used as diagnostic indicators of LEAD.

Keywords lower extremity arterial disease; type 2 diabetes mellitus; glycosylated hemoglobin; low-density lipoprotein cholesterol

2型糖尿病(type 2 diabetes mellitus, T2DM)是常见的慢性疾病, 据估计, 全球T2DM患者超1.7亿^[1]。数据^[2-3]显示: 我国50岁以上T2DM患者1年内糖尿病足溃疡发生率高达31.6%, 且糖尿病足所致截肢占全部截肢的27.3%, 而截肢患者5年内病死率高达40.0%, 糖尿病足给患者家庭及社会造成巨大压力。下肢动脉病变(lower extremity arterial disease, LEAD)作为T2DM患者的常见慢性并发症, 是糖尿病足的主要病因, 以下肢血管狭窄或闭塞为主要表现^[4]。在临床中, 许多T2DM下肢动脉病变的患者, 由于缺少典型的间歇性跛行或静息痛的症状没有得到及时诊断, 因此探讨有效的诊断标志物显得尤为必要。动脉粥样硬化(atherosclerosis, AS)是LEAD发生和发展的基础。研究^[5]表明: 胰岛素抵抗(insulin resistance, IR)、高血糖状态、脂代谢紊乱等均与AS关系密切。糖化血红蛋白(glycosylated hemoglobin, HbA1c)水平能够反映糖代谢状况, 与血糖水平呈正相关。有研究^[6]显示: HbA1c对血管并发症有预测作用。低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)是公认的AS危险因素, 为常用的心血管疾病发病和预后的评估指标^[7-8]。目前, 关于HbA1c、LDL-C与糖尿病LEAD关系的研究尚少, 他们之间的相关性有待明确。本研究旨在通过观察T2DM合并LEAD患者血清HbA1c、LDL-C水平变化, 分析HbA1c、LDL-C与LEAD之间的相关性, 为LEAD的诊断提供一定理论依据。

1 对象与方法

1.1 对象

选取2018年5月至2021年5月华东师范大学附属芜湖医院收治的T2DM患者96例。纳入标准: 1)符合1999年WHO糖尿病诊断标准; 2)年龄 ≥ 18 岁。排除标准: 1)1型糖尿病; 2)肝肾功能障碍; 3)心脑血管病史; 4)甲状腺疾病; 5)恶性肿瘤; 6)妊娠及哺乳期女性; 7)存在引起下肢动脉病变的非糖尿病因素。参照《中国2型糖尿病防治指南(2017年版)》^[3], 按双下肢彩超是否合并血管斑块, 将患者分为单纯T2DM组($n=47$)与T2DM合并LEAD组($n=49$)。本研究获得华东师范大学附属芜湖医院医学伦理委员会审批[审批号: (2022)医学伦审第(14)号], 研究对象均签署知情同意书。

1.2 方法

收集患者性别、年龄、病程、体重指数、吸烟史、高血压病史等一般资料。患者空腹8 h后, 采集血标本5 mL, 300 r/min离心10 min, 收集上清液于 $-80\text{ }^{\circ}\text{C}$ 保存。采用全自动生化分析仪(贝克曼IU5800)进行检测, 采用去游离法检测三酰甘油(triglyceride, TG), 酶法测定总胆固醇(total cholesterol, TC)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C), 选择性可融化法测定LDL-C(美国贝克曼公司试剂盒, 批号9193), 酶法测定空腹血糖(fasting

plasma glucose, FPG), 高效液相层析法测定 HbA1c (东曹全自动糖化血红蛋白分析仪 HLC-723G8 及原装配套试剂, 批号 1E1362)。采用 GE VIVID E9 超声诊断仪检测双下肢血管是否合并下肢血管斑块。

1.3 统计学处理

应用 SPSS 24.0 统计软件分析数据。满足正态分布的计量资料以均数±标准差($\bar{x}\pm s$)表示, 组间对比用独立样本 t 检验; 计数资料比较用 χ^2 检验; 采用多元逐步回归分析 T2DM 患者下肢血管病变与 LDL-C、HbA1c 的相关性; 应用受试者工作特征(receiver operating characteristic, ROC)曲线评价 HbA1c、LDL-C 对 LEAD 的诊断能力。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组临床资料比较

两组 FPG、HbA1c、TC、TG、LDL-C 水平和

合并高血压比例差异均有统计学意义(均 $P<0.05$); 两组年龄、性别、病程等其他临床资料对比差异无统计学意义($P>0.05$, 表 1)。

2.2 多元逐步回归分析

对 T2DM 患者下肢血管病变的相关因素 LDL-C、HbA1c、年龄、性别、病程、是否患高血压病、是否吸烟、FPG、TC、TG、HDL-C 作为自变量进行逐步多元回归分析, 结果发现 T2DM 患者下肢血管病变与 LDL-C、HbA1c、年龄相关($P<0.05$, 表 2)。

2.3 ROC 曲线分析

LDL-C 的 ROC 曲线下面积为 0.727($P<0.05$), LDL-C 值可作为 T2DM 患者下肢血管病变的诊断依据, 诊断效能中等。HbA1c 的 ROC 曲线下面积为 0.680($P<0.05$), HbA1c 值可作为 T2DM 患者下肢血管病变的诊断依据, 诊断效能中等。二者联合诊断的效能进一步提高, 其曲线下面积为 0.757(表 3)。ROC 曲线见图 1。

表 1 两组临床资料比较

Table 1 Comparison of clinical data between the two groups

指标	单纯 T2DM 组($n=47$)	T2DM 合并 LEAD 组($n=49$)	t/χ^2	P
年龄/岁	66.17 ± 10.59	64.02 ± 10.55	-0.996	0.322
性别/[例(%)]			1.609	0.223
男	30 (63.83)	25 (51.02)		
女	17 (36.17)	24 (48.98)		
病程/年	10.20 ± 7.84	11.97 ± 7.31	1.143	0.256
高血压病/[例(%)]			7.524	0.009
是	25 (53.19)	39 (74.36)		
否	22 (46.81)	10 (25.64)		
吸烟/[例(%)]			3.977	0.066
是	5 (10.64)	13 (26.53)		
否	42 (89.36)	36 (73.47)		
FPG/(mmol·L ⁻¹)	9.48 ± 3.05	7.41 ± 2.99	-3.345	0.001
TC/(mmol·L ⁻¹)	5.08 ± 1.10	4.50 ± 0.99	-2.721	0.008
TG/(mmol·L ⁻¹)	2.33 ± 2.33	1.45 ± 0.86	-2.494	0.014
HDL-C/(mmol·L ⁻¹)	1.20 ± 0.31	1.26 ± 0.27	1.050	0.296
LDL-C/(mmol·L ⁻¹)	2.71 ± 0.83	3.69 ± 2.62	2.462	0.016
HbA1c/%	8.12 ± 1.54	9.93 ± 2.08	5.022	<0.001

表2 T2DM患者下肢血管病变的多元回归分析

Table 2 Multiple regression analysis of lower extremity arterial disease in T2DM

变量	回归系数	标准误	标准回归系数	t	P
年龄	0.011	0.005	0.222	2.127	0.036
性别	0.003	0.104	0.003	0.031	0.976
病程	-0.007	0.007	-0.099	-1.003	0.319
是否患高血压病	-0.031	0.095	-0.031	-0.327	0.744
是否吸烟	-0.212	0.128	-0.166	-1.666	0.099
FPG	0.022	0.016	0.140	1.408	0.163
TC	0.054	0.059	0.116	0.911	0.365
TG	0.028	0.031	0.102	0.911	0.365
HDL-C	-0.221	0.218	-0.128	-1.011	0.315
LDL-C	-0.055	0.022	-0.220	-2.493	0.015
HbA1c	-0.091	0.024	-0.355	-3.823	<0.001

R=0.635.

表3 HbA1c、LDL-C诊断T2DM患者下肢血管病变的ROC曲线分析结果

Table 3 Results of ROC curve analysis on HbA1c and LDL-C in diagnosis of lower extremity vascular disease in T2DM patient

指标	截断值	曲线下面积	标准误	P	渐近95%CI		敏感度/%	特异度/%
					下限	上限		
HbA1c	8.55%	0.680	0.052	<0.001	0.577	0.772	60.0	70.6
LDL-C	2.69 mmol/L	0.727	0.048	<0.001	0.627	0.813	61.2	76.5
二者联合		0.757	0.050	<0.001	0.658	0.838	64.4	80.4

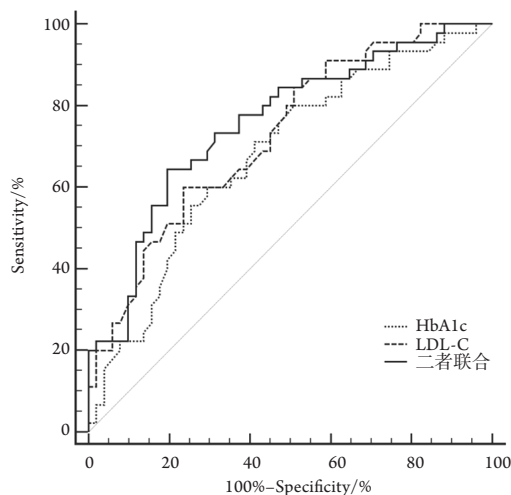


图1 HbA1c、LDL-C及其联合对下肢血管病变诊断的ROC曲线图

Figure 1 ROC curve of HbA1c, LDL-C and their combination in diagnosis of lower extremity vascular disease

3 讨论

T2DM患者发生LEAD的风险相比健康人明显增高^[9]。AS是LEAD的关键病理基础，而高血糖、高血脂是AS的危险因素，并且血脂异常是糖尿病与糖尿病动脉血管并发症之间的主要联系^[10-11]。本研究显示：两组FPG、HbA1c、TC、TG、LDL-C水平有显著差异，提示血糖、血脂异常与LEAD发生相关，与上述理论一致。

HbA1c是糖尿病患者监控血糖的重要指标^[12]。高HbA1c水平已被证实是糖尿病和AS的危险因素，这可能是由于高HbA1c能够使得氧自由基大量产生，促进LDL氧化，致使血管内皮细胞发生损伤^[13]。此外，高HbA1c水平还可诱导动脉内膜下脂质非正常沉积与变性，促进内膜平滑肌增生、纤维化，最终形成斑块^[14]。本研究logistic回归分析显示：血清HbA1c与T2DM患者发生LEAD相关，提示

HbA1c可能促进了LEAD的发生和发展。左红等^[15]也得出类似结论,其通过对176例T2DM患者血清HbA1c水平进行检测并分析发现,HbA1c是T2DM患者心血管并发症的危险因素。因此,应密切监测T2DM患者血清HbA1c水平,以早期筛查LEAD的发生风险,并及时干预。

LDL-C致AS的机制为LDL-C容易在动脉壁内膜沉积,并且容易与糖蛋白结合,促进胆固醇在血管壁的沉积;LDL-C水平增高时可被氧化修饰形成氧化LDL,诱导巨噬细胞不断摄入脂质,引起血管内皮细胞损伤,在局部水解能够产生促炎因子和趋化因子,激活一系列信号通路进而促进AS的形成^[16]。此外,LDL-C还能诱导血栓素2的形成,促进血小板聚集,从而对斑块形成有强大的促进作用^[17]。研究^[18]表明:LDL-C是T2DM患者大血管并发症的危险因素。本研究结果表明:血清LDL-C水平与T2DM患者发生LEAD密切相关,提示LDL-C可能参与了T2DM患者LEAD的病理过程,监测患者LDL-C水平变化,可能有助于早期筛查LEAD,对临床防治有指导意义。此外,本研究还应用ROC曲线评价了HbA1c、LDL-C对LEAD的诊断能力,结果显示:HbA1c、LDL-C均对T2DM患者发生LEAD有中等效能的诊断能力,曲线下面积分别为0.680、0.727,且二者联合可进一步提高诊断效能。由于HbA1c、LDL-C检测方法简便,成本低,在临床应用已成熟,具有较好的统一性和规范性,因此有望作为早期预测LEAD发生的指标。

本研究也存在局限性:首先,样本量较小,统计分析难免存在偏差,HbA1c、LDL-C与LEAD的相关性仍有待多中心、大样本量的研究分析;其次,降糖降脂治疗的效果与HbA1c、LDL-C的靶水平尚不清楚,这是今后的研究方向。

综上,在T2DM患者中,血清HbA1c、LDL-C水平与LEAD发生相关,其水平增高对于提示LEAD风险有重要临床意义。通过检测血清HbA1c、LDL-C水平,可能有助于进行风险预测,早期发现LEAD,早干预,以改善患者预后。

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