doi: 10.3978/j.issn.2095-6959.2022.07.017
View this article at: https://dx.doi.org/10.3978/j.issn.2095-6959.2022.07.017

HbA1c、LDL-C与2型糖尿病下肢动脉血管病变的相关性

何琏，盛昭，季学磊

(华东师范大学附属芜湖医院内分泌科，安徽 芜湖 241000)

[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

HE Lian, SHENG Zhao, JI Xuelei

(Department of Endocrinology, Wuhu Hospital Affiliated to East China Normal University, Wuhu Anhui 241000, China)

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

收稿日期 (Date of reception)：2021−12−31
通信作者 (Corresponding author)：何琏，Email: zxwerx@163.com

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：2017026)，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 ℃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，批号IE1362)。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

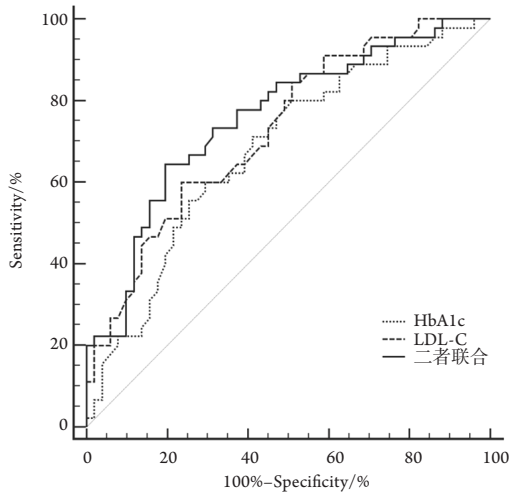

图1 HbA1c、LDL-C及其联合对下肢血管病变诊断的ROC曲线图

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，这可能是因为高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。

参考文献

1. Dinesh SA, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people[J]. Lancet, 2015, 385(suppl 1): S86.
2. Jiang Y, Wang X, Lei X, et al. A cohort study of diabetic patients and diabetic foot ulceration patients in China[J]. Wound Repair Regen, 2015, 23(2): 222-230.
3. 中华医学会糖尿病学分会. 中国2型糖尿病防治指南(2017年版)[J]. 中国实用内科杂志, 2018, 38(4): 292-344.
   Chinese diabetes society. Guidelines for the prevention and control of type 2 diabetes in China (2017 edition)[J]. Chinese Journal of Practical Internal Medicine, 2018, 38(4): 292-344.
4. Mueller T, Hinterreiter F, Poelz W, et al. Mortality rates at 10 years are higher in diabetic than in non-diabetic patients with chronic lower extremity peripheral arterial disease[J]. Vasc Med, 2016, 21(5): 445-452.
5. Lu MC, Hsu H, Lin CH, et al. Systemic vasculitis is associated with a higher risk of lower extremity amputation in patients with severe peripheral arterial occlusive disease: a secondary analysis of a nationwide, population-based health claims database[J]. Rheumatol Int, 2017, 37(11): 1847-1852.
6. 邢美艳, 王贻坤, 夏营威, 等. 皮肤无创晚期糖基化终末产物测定在社区2型糖尿病血管性并发症筛查中的作用研究[J]. 中国全科医学, 2020, 23(8): 913-919.
   XING Meiyan, WANG Yikun, XIA Yingwei, et al. Value of advanced glycation end-products in skin measured noninvasively in community-based screening of type 2 diabetes-related vascular complications[J]. Chinese General Practice, 2020, 23(8): 913-919.
7. 杨芬, 苏冠华, 程翔. 干预低密度脂蛋白胆固醇是动脉粥样硬化性心血管病防治的根本措施[J]. 中华心血管病杂志, 2021, 49(6): 638-642.
   YANG Fen, SU Guanhua, CHENG Xiang. Management of low-density lipoprotein cholesterol is fundamental for prevention and treatment of atherosclerotic cardiovascular disease[J]. Chinese Journal of Cardiology, 2021, 49(6): 638-642.
8. 罗兰, 董春江, 李欣宇, 等. 大连地区居民非高密度脂蛋白胆固醇,低密度脂蛋白胆固醇与心血管危险因素聚集的相关性研究[J]. 中华糖尿病杂志, 2020, 12(11): 885-900.
   LUO Lan, DONG Chunjiang, LI Xinyu, et al. Association of non-high density lipoprotein cholesterol, low density lipoprotein cholesterin and cardiovascular risk factors in the residents of Dalian[J]. Chinese Journal of Diabetes Mellitus, 2020, 12(11): 885-900.
9. 杨毅, 冉兴无. 2型糖尿病患者下肢血管病变与蛋白尿的相关性研究[J]. 中国糖尿病杂志, 2016, 24(12): 1065-1068.
   YANG Yi, RAN Xingwu. Relationship between albuminuria and lower-extremity arterial disease in patients with type 2 diabetes mellitus[J]. Chinese Journal of Diabetes, 2016, 24(12): 1065-1068.
10. Luo J, Xu Q, Jiang B, et al. Selectivity, cell permeability and oral availability studies of novel bromophenol derivative HPN as protein tyrosine phosphatase 1B inhibitor[J]. Br J Pharmacol, 2018, 175(1): 140-153.

11. 王怡萌, 栾波, 郭鹏, 等. 血脂沉积指数与冠心病动脉粥样硬化的相关性研究[J]. 中国动脉硬化杂志, 2020, 28(7): 584-588.
WANG Yimeng, LUAN Bo, GUO Peng, et al. Study on the relationship between lipid deposition index and atherosclerosis of coronary heart disease[J]. Chinese Journal of Arteriosclerosis, 2020, 28(7): 584-588.
12. 郭哲, 宁金月, 王玉沙. 2型糖尿病患者BMI与HbAlc, 胰岛素抵抗及肾损害指标的相关性分析[J]. 川北医学院学报, 2020, 35(2): 297-300.
GUO Zhe, NING Jinyue, WANG Yusha. Correlations among the BMI and HbAlc, the insulin resistance and the renal damage indexes in patients with T2DM[J]. Journal of North Sichuan Medical College, 2020, 35(2): 297-300.
13. 许爱华, 吕瑾. 糖尿病并发心梗患者糖化血红蛋白水平和预后心功能的关系[J]. 湖南师范大学学报(医学版), 2021, 18(1): 88-90.
XU Aihua, LÜ Jin. The relationship between glycosylated hemoglobin level and prognosis of cardiac function in patients with diabetes complicated with myocardial infarction[J]. Journal of Hunan Normal University. Medical Edition, 2021, 18(1): 88-90.
14. 刘道利, 李鸯, 邱芳华, 等. 血清胱抑素C和糖化血红蛋白水平变化与颈动脉粥样硬化的相关性分析[J]. 检验医学与临床, 2019, 16(8): 13-16.
LIU Daoli, LI Yang, QIU Fanghua, et al. Correlation analysis between serum levels of cystatin C and glycated hemoglobin in patients with carotid artery atherosclerosis[J]. Laboratory Medicine and Clinic, 2019, 16(8): 13-16.
15. 左红, 王述进, 冯佳, 等. 血清总胆红素、糖化白蛋白、糖化血红蛋白与糖尿病血管并发症的关系[J]. 中国动脉硬化杂志, 2019, 27(9): 787-790.
ZUO Hong, WANG Shujin, FENG Jia, et al. The relationship between serum total bilirubin, glycated albumin, glycated hemoglobin and diabetic vascular complications[J]. Chinese Journal of Arteriosclerosis, 2019, 27(9): 787-790.
16. Fernandez-Cidon B, Pinto-Sala X, Ribalta-Vives J, et al. Diagnostic accuracy of a novel predictive model for ischemic events based on small dense LDL-cholesterol concentration (SDLDL-C) and lipid characterization by NMR[J]. Clin Chim Acta, 2019, 493: S81-S82.
17. Ofori-Asenso R, Zoungas S, Tonkin A, et al. LDL-cholesterol is the only clinically relevant biomarker for atherosclerotic cardiovascular disease (ASCVD) risk[J]. Clin Pharmacol Ther, 2018, 104(2): 235-238.
18. 曾青青, 王文, 冯红, 等. 糖尿病性大血管病变患者血压,低密度脂蛋白胆固醇及糖化血红蛋白水平变化情况[J]. 实用心脑肺血管病杂志, 2020, 28(S1): 98-99.
ZENG Qingqing, WANG Wen, FENG Hong, et al. Changing of blood pressure and LDL-C, HbA1c levels in patients with diabetic macroangiopathy[J]. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease, 2020, 28(S1): 98-99.

本文引用： 何琏, 盛昭, 季学磊. HbA1c、LDL-C与2型糖尿病下肢动脉血管病变的相关性[J]. 临床与病理杂志, 2022, 42(7): 1629-1634. doi: 10.3978/j.issn.2095-6959.2022.07.017
Cite this article as: HE Lian, SHENG Zhao, JI Xuelei. Correlation between HbA1c, LDL-C and lower extremity arterial disease in type 2 diabetes mellitus[J]. Journal of Clinical and Pathological Research, 2022, 42(7): 1629-1634. doi: 10.3978/j.issn.2095-6959.2022.07.017