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【应用研究】

糖尿病视网膜病变与外周血管和心血管病变的相关性研究

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【摘要】 **目的**　探讨2型糖尿病患者发生糖尿病视网膜病变(diabetic retinopathy,DR)的危险因素,以及这些危险因素与外周血管疾病(peripheral arterial disease,PAD)和心血管疾病(cardiovascular disease,CVD)之间的关系。**方法**　将1243例2型糖尿病患者分为无糖尿病视网膜病变患者(Non-DR)组847例、非增生型DR(NPDR)组317例、增生型DR(PDR)组79例,收集年龄、性别、2型糖尿病病程、CVD、脑血管疾病、高血压病史、吸烟饮酒史、身体质量指数(body mass index,BMI)、收缩压(systolic blood pressure,SBP)、舒张压(diastolic pressure,DBP)等一般资料。测定所有患者空腹血糖(fasting blood sugar,FBG)、甘油三酯(triglycerides,TG)、总胆固醇(total cholesterol,TC)、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)、糖化血红蛋白[hemoglobin(Hb)A1c,HbA1C]。采用无创性的血管筛检装置收集踝肱指数(ankle-brachial index,ABI)数值,且ABI<0.9或≥1.3被诊断为PAD。采用高分辨率B型超声筛查两侧颈部、股浅动脉、股动脉、胭动脉、胫前后动脉斑块。**结果**　与Non-DR组相比较,NPDR组和PDR组2型糖尿病病程更长,SBP、TC、LDL-C均更高。与NPDR组比较,PDR组TC、SBP、LDL-C均更高,且糖尿病病程更长,差异均有统计学意义(均为$P<0.05$),但三组之间BMI、HbA1c、TG、HDL-C水平比较差异均无统计学意义(均为$P>0.05$)。Non-DR组、NPDR组、PDR组异常ABI发生率分别为7.20%、10.90%、13.89%,结果提示随着DR病变的加重,异常ABI发生率逐渐升高($P<0.05$)。Non-DR组、NPDR组、PDR组外周动脉斑块发生率分别为68.00%、81.40%、87.20%,提示随着DR病变的加重,与Non-DR组比较,NPDR组和PDR组更容易患PAD($P<0.001$)。将性别、年龄、糖尿病病程、冠心病、脑血管疾病、ABI、外周动脉斑块、SBP≥130 mmHg(1 kPa=7.5 mmHg)、HbA1c、TC、TG、HDL-C、LDL-C水平、吸烟史、饮酒史纳入多元线性回归分析,结果发现外周动脉斑块($r=2.15$)、SBP≥130 mmHg($r=1.50$)、高胆固醇血症($r=1.72$)、高糖化血红蛋白($r=2.24$)均是DR的危险因素(均为$P<0.05$)。**结论**　在2型糖尿病患者中,DR与PAD、CVD密切相关,而高胆固醇血症是DR、PAD和CVD的共同危险因素。在PDR患者中,PAD和CVD的患病率均明显高于NPDR,因此DR患者应及时进行ABI、超声检查和血脂检查,将有助于尽早识别和预防系统性血管疾病。

【关键词】 糖尿病视网膜病变;外周血管疾病;心血管疾病;2型糖尿病;危险因素
【中图分类号】 R774.1

中国慢性病及其危险因素监测报告显示,18岁以上成年人糖尿病的患病率为11.6%,糖尿病前期人群所占比例同样高。然而,这些患者的知晓率仅为30.1%,且控制率仅为39.7%。此外,更为严重的是,糖尿病导致的糖尿病视网膜病变(diabetic retinopathy,DR)是导致视力丧失的主要原因。同时,DR患者的外周血管疾病(peripheral arterial disease,PAD)和心血管疾病(cardiovascular disease,CVD)发生率将显著增加[1-2]。这些糖尿病的并发症已经成为中国公共卫生健康的严峻挑战。2型糖尿病可导致大血管和微血管病变[3-4]。PAD是动脉粥样硬化引起的一种主要动脉疾病,PAD患者下肢血流减少,最终可能导致截肢[1],其发病率与年龄和心血管事件密切相关[5-6]。近年来研究认为,高血压、高血糖、血脂异常、糖尿病病程在PAD、CVD合并DR患者的发病和进展中具有重要作用[7-8],但DR与PAD、CVD之间的关系仍未能完全明了[9-10]。因此,本研究观察2型糖尿病患者的潜在危险因素,评估危险因素与DR的发生与进展之间的关系,从而进一步分析其与PAD、CVD之间的相关性。

1　资料与方法

1.1　一般资料　选取2014年9月至2018年8月在本院住院且诊断为2型糖尿病患者1243例,所有患者均经内分泌科医师确诊为2型糖尿病[11],眼科常规检查后行眼底荧光血管造影检查确立DR诊断[12],同时由经验丰富的眼科临床医师根据世界卫生组织制定的DR分期标准进行分级[12];其中无DR(Non-DR)组患者847例,其中男508例、女339例,年龄(57.42±12.77)岁;非增生型DR(non-proliferative diabetic retinopathy,NPDR)组317例,其中男212例、女105例,年龄(58.95±11.22)岁;增生型DR(proliferative diabetic retinopathy,PDR)组79例,其中男35例、女44例,年龄(57.38±10.95)岁。所有病例均排除1型糖尿病、急性肾损伤、糖尿病酮症酸中毒、急性高血糖症状(伴有重度酮尿)、急性感染、白内障。3组间研究对象的年龄、性别构成比较,差异均无统计学意义(均为$P>0.05$)。

1.2 方法

1.2.1 实验室指标 记录所有研究对象的年龄、性别、2型糖尿病病程、CVD、脑血管疾病、高血压病史、吸烟饮酒史、体质量指数(body mass index,BMI)、收缩压(systolic blood pressure,SBP)、舒张压(diastolic pressure,DBP)等一般资料。受检者禁食8~10 h后晨起空腹取肘正中静脉血,用全自动生化分析仪测定空腹血糖(fasting blood sugar,FBG)、甘油三酯(triglycerides,TG)、总胆固醇(total cholesterol,TC)、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)、糖化血红蛋白[hemoglobin(Hb)A1c,HbA1C]。

1.2.2 踝肱指数 踝肱指数(ankle-brachial index,ABI)是诊断PAD患者动脉粥样硬化的良好指标,ABI<0.9提示周围动脉闭塞性疾病[13],ABI>1.3提示内侧动脉钙化[7]。相关研究报告,ABI<0.9或ABI>1.3是临床应用中预测心血管事件发病率和死亡率的独立标志物[8]。本研究采用无创性的血管筛检装置(BP-203,Omron,Kyoto,日本)收集ABI数值,且ABI<0.9或ABI≥1.3被诊断为PAD。

1.2.3 外周动脉斑块 采用高分辨率B型超声筛查两侧颈部、股浅动脉、股动脉、腘动脉、胫前后动脉。

1.3 统计学方法 采用SPSS 20.0统计学软件进行统计分析。计量资料用$\bar{x}\pm s$表示,对于偏态分布资料,采用中位数表示;对于正态分布资料,采用方差分析检验,方差不齐时采用秩和检验,相关性分析采用Pearson相关性分析。分类变量采用卡方检验,3组间的两两比较采用q检验;采用Logistic回归分析确定DR的相关因素。检验水准:$\alpha=0.05$。

2 结果

2.1 3组一般资料比较 与Non-DR组相比较,NPDR组和PDR组患者2型糖尿病病程更长,SBP、TC、LDL-C均更高(均为$P<0.05$)。与NPDR组比较,PDR组TC、SBP、LDL-C均更高,且糖尿病病程更长,差异均有统计学意义(均为$P<0.05$,见表1),但3组之间BMI、HbA1c、TG、HDL-C水平比较差异均无统计学意义(均为$P>0.05$)。

表1 三组临床指标比较

变量	Non-DR组($n=847$)	NPDR组($n=317$)	PDR组($n=79$)	P值
年龄/岁	57.42±12.77	58.95±11.22	57.38±10.95	0.423
糖尿病病程/a	7.61±6.46	11.03±7.00	11.68±6.62	0.000
冠心病病史	14.50%	15.95%	12.82%	0.671
脑血管病史	10.87%	13.62%	13.64%	0.380
高血压病史	46.56%	50.17%	52.27%	0.440
有饮酒史患者百分比	28.07%	28.24%	15.91%	0.205
有吸烟史患者百分比	43.59%	47.18%	38.64%	0.407
收缩压/mmHg	134.60±18.14	139.41±21.15	148.55±24.48	0.001
舒张压/mmHg	79.87±12.14	79.02±11.91	79.59±12.21	0.465
BMI/kg·m^{-2}	24.50(22.60~26.80)	24.60(22.40~26.73)	24.60(21.65~26.85)	0.883
HbA1C	(9.42±4.13)%	(9.54±2.24)%	(9.40±2.60)%	0.105
TC/mmol·L^{-1}	4.37±1.45	4.41±1.27	4.44±1.35	0.042
TG /mmol·L^{-1}	1.55(1.03,2.38)	1.46(1.02,2.25)	1.49(0.93,2.62)	0.583
HDL-C/mmol·L^{-1}	1.04(0.86,1.29)	1.08(0.87,1.31)	1.12(0.93,1.51)	0.153
LDL-C/mmol·L^{-1}	2.60±0.91	2.68±1.02	2.70±1.09	0.030

注:1 kPa=7.5 mmHg

2.2 3组之间异常ABI比较 Non-DR组异常ABI 61例,正常ABI 786例,异常ABI发生率为7.20%;NPDR组异常ABI 35例,正常ABI 282例,异常ABI发生率为10.90%,PDR组异常ABI 11例,正常ABI 68例,异常ABI发生率为13.89%。随着DR病变的加重,异常ABI发生率逐渐升高,差异有统计学意义($P<0.05$)。

2.3 3组之间外周动脉斑块比较 Non-DR组、NPDR组、PDR组中检查出外周动脉斑块的患者分别有576例、258例、69例,Non-DR组、NPDR组、PDR组外周动脉斑块发生率分别为68.00%、81.40%、87.20%,结果提示随着DR病变的加重,与Non-DR组比较,NPDR组和PDR组更容易患PAD,差异有统计学意义($P<0.001$)。

2.4 DR相关影响因素的多元线性回归分析 见表2。将性别、年龄、糖尿病病程、冠心病、脑血管病、

表2 DR相关影响因素的多元线性回归分析

变量	OR(95% CI)	P值
性别(男/女)	1.20(0.80~1.65)	0.309
年龄	0.96(0.95~0.99)	0.001
糖尿病病程	1.24(1.05~1.30)	0.007
冠心病病史	0.98(0.64~1.42)	0.758
脑血管病史	1.20(0.83~1.85)	0.295
ABI	1.69(0.92~2.28)	0.092
外周动脉斑块	2.15(1.54~2.98)	0.002
收缩压≥130 mmHg	1.50(1.16~2.01)	0.001
HbA1C	2.24(1.32~3.32)	0.001
TC	1.72(0.90~2.28)	0.002
TG	0.91(0.62~1.05)	0.205
HDL-C	1.27(0.63~2.21)	0.685
LDL-C	0.85(0.57~1.25)	0.326
吸烟史	1.21(1.00~1.02)	0.258
饮酒史	0.99(0.98~1.00)	0.154

ABI、外周动脉斑块、SBP≥130 mmHg、HbA1c、TC、TG、HDL-C、LDL-C、吸烟史、饮酒史纳入多元线性回归分析发现，外周动脉斑块、SBP≥130 mmHg、高胆固醇血症、高 HbA1C 是 DR 的危险因素，差异均有统计学意义（均为 $P<0.05$）。

3 讨论

近年来 ABI 广泛被临床工作者认同为诊断 PAD 和 CVD 的重要指标[14-15]。ABI 值低于正常范围被认为与全身动脉粥样硬化相关，同时也并被认为是 CVD 发病率和死亡率的主要危险因素[16]。Li 等[17]发现当 ABI<0.9 时，调整后的 CVD 死亡率的相对风险显著增加，且该风险随着 ABI 的降低逐渐增高。此外，研究显示异常高的 ABI 值也被用来预测糖尿病患者的全身和心血管死亡率[18]。Tsuchiya 等[19]认为 ABI 的增加与冠状动脉钙化密切相关，同时也可反映弥漫性动脉粥样硬化性疾病。同时，Mcdermott 等[20]发现相比于 ABI 值正常的患者，ABI 临界值的患者颈动脉内膜-中膜厚度更容易增厚，且冠状动脉钙化评分>20 的风险增加。因此，本研究显示，随着 DR 病变程度的加重，异常 ABI 发生率将逐渐增加，同时 PAD 的发生率也逐渐增加，提示异常 ABI 的发生率与 DR 严重程度密切相关。

通过超声检查外周动脉斑块是临床应用诊断 PAD 的准确评估工具。然而，目前尚缺乏对 DR 不同分期的外周动脉斑块患病率分析，本研究通过超声检查外周动脉斑块，比较 Non-DR 组、NPDR 组和 PDR 组的差异，结果显示 NPDR 组和 PDR 组外周动脉斑块发生率明显高于 Non-DR 组，同时通过多元线性回归分析，本研究发现外周动脉斑块和 SBP ≥ 130 mmHg 是 DR 的危险因素。研究发现，在血压波动过程中，覆盖血管壁内表面的内皮细胞可以产生、激活和释放各种血管活性物质，从而进一步导致动脉的结构和功能改变[21]。Krishnan 等[22]认为随着动脉弹性和血管顺应性的降低（PAD 和 CVD 的早期病理改变），SBP 增加，同时高血压是导致中风和急性冠状动脉事件的主要原因。本研究发现，DR 患者 PAD 发生率增加，通过 ABI 和超声检查对 DR 患者进行早期筛查，将有助于降低 PAD 和 CVD 的发生率。

近年来越来越多的研究发现，大血管病变和微血管病变密切相关，且具有一些共同的危险因素[23]。Kim 等[24]认为 2 型糖尿病患者往往血脂异常，引发动脉粥样硬化，进一步导致 PAD 和 CVD。尽管目前一些研究发现动脉粥样硬化与 DR 之间具有相同危险因素，但两者之间的关系尚缺乏准确定义。本研究通过对 DR 病变程度进行分期研究发现，与 Non-DR 组相比，NPDR 组和 PDR 组 TC 和 LDL-C 均升高。通过对 DR 的相关影响因素进行多元线性回归分析，我们发现血脂异常是导致 DR 微血管病变的重要危险因素。Valensi 等[25]认为血脂异常同样也是导致大血管病变的主要因素，在无临床症状的糖尿病患者中，TG 升高和 HDL-C 降低是患者冠心病或无症状心肌缺血发生的主要原因。Giordano 等[26]研究认为，血脂异常将引起氧自由基增加，NO 失活，即氧化应激反应，最终导致血管内皮功能障碍，引发大血管和微血管病变。本研究发现，血脂异常是 PAD、CVD 和 DR 的共同危险因素，结果提示在 DR 患者中，早期筛查和控制异常血脂将有助于预防和延缓大血管和微血管病变的发生和进展，从而降低 PAD 和 CVD 的发生风险。

综上所述，在 2 型糖尿病患者中，DR 与 PAD、CVD 密切相关，而高胆固醇血症是 DR、PAD 和 CVD 的共同危险因素。在 PDR 患者中，PAD 和 CVD 的患病率均明显高于 NPDR，因此 DR 患者应及时完善 ABI、超声检查和血脂检查，将有助于尽早识别和预防系统性血管疾病。

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Correlation of diabetic retinopathy with peripheral vascular disease and cardiovascular disease

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【Abstract】 **Objective** To explore risk factors of occurring diabetic retinopathy (DR) in patients with type 2 diabetes (T2D), and correlation of these risk factors with peripheral arterial disease (PAD) and cardiovascular disease (CVD). **Methods** Totally 1243 T2D patients were classified as Non-DR (847 patients), non-proliferative DR (NPDR; 317 patients) and proliferative DR (PDR; 79 patients). General data were collected, including age, gender, course of T2D, CVD, cardiovascular disease, history of hypertension, history of alcohol drinking and smoking, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP), etc. Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), hemoglobin A1c (HbA1C) were detected in all patients. Ankle-branchial index (ABI) was measured with noninvasive vascular screening device. The patient with ABI < 0.9 or ≥1.3 was diagnosed of PAD. High-resolution B ultrasound was used to detect plaques at both sides of neck, superficial femoral artery, femoral artery, popliteal artery, anterior and posterior tibial artery. **Results** Compared with non-DR group, patients with NPDR and PDR had longer course of T2D, higher SBP, TC and LDL-C. Compared with NPDR group, patients with PDR had higher TC, SBP and LDC-C, and longer course of T2D (all $P < 0.05$). No statistical difference was found in BMI, HbA1c, TG or HDL-C among three groups (all $P > 0.05$). The incidences of abnormal ABI were 7.20%, 10.90% and 13.89% in Non-DR, NPDR and PDR groups, respectively. With the aggravation of DR lesions, the incidence of abnormal ABI gradually increased ($P < 0.05$). The incidences of peripheral arterial plaques were 68.00%, 81.40% and 87.20% in Non-DR, NPDR and PDR groups, respectively. Compared with Non-DR group, patients with NPDR and PDR were more likely to have PAD with aggravation of DR lesions ($P < 0.001$). Logistic regression analysis was taken to explore the correlation among sex, gender, course of T2D, coronary heart disease, cardiovascular diseases, ABI, peripheral arterial plaques, SBP ≥130 mmHg (1 kPa = 7.5 mmHg), HbA1c, TC, TG, HDL-C, LDL-C, smoking history and history of alcohol drinking. The results showed that peripheral arterial plaques ($r = 2.15$), SBP ≥130 mmHg ($r = 1.50$), hypercholesteremia ($r = 1.72$), high glycosylated hemoglobin ($r = 2.24$) were risk factors of DR (all $P < 0.05$). **Conclusion** In patients with T2D, DR is closely related to PAD and CVD. Hypercholesterolemia is a common risk factor for DR, PAD and CVD. In patients with PDR, the prevalence of PAD and CVD is significantly higher than that of patients with NPDR. Therefore, we emphasize the recommendation of performing the ABI test, ultrasonography and lipid profile in DR patients in time, which will help to identify and prevent systemic vascular diseases as soon as possible.

【Key words】 diabetic retinopathy; peripheral arterial disease; cardiovascular disease; type 2 diabetes; risk factor