2型糖尿病患者血清CTRP9水平与糖尿病视网膜病变的相关性

周鹏鹏[1,2],刘丽燕[1],高卫萍[2]
[1]南京中医药大学附属昆山市中医医院,江苏 昆山 215300;[2]南京中医药大学,江苏 南京 210029

摘要:目的 探讨2型糖尿病(T2DM)患者血清C1q肿瘤坏死因子相关蛋白9(CTRP9)水平与糖尿病视网膜病变(DR)的关系。**方法** 根据纳入标准收集291例T2DM患者临床资料,按照眼底检查结果分为DR组与非DR (NDR)组,ELISA法检测血清CTRP9、脂联素及胰岛素水平。统计分析血清CTRP9水平与T2DM患者、T2DM并发DR患者临床资料的相关性,探讨血清CTRP9水平与T2DM患者并发DR的关系。**结果** 与NDR组相比,DR组血清CTRP9水平显著升高(P<0.001);血清脂联素水平显著降低(P<0.001)。Pearson相关性分析显示T2DM并发DR患者中,血清CTRP9水平与DR严重程度呈显著正相关(P<0.05);与血清脂联素水平呈负相关(P=0.017)。多元Logistic回归分析校正年龄、性别、体重指数、糖尿病病程、糖化血红蛋白、空腹血糖、空腹胰岛素、HOMA-IR、高血压病史、收缩压、低密度脂蛋白、甘油三酯等混杂因素,随着血清CTRP9水平的升高,T2DM并发DR的风险显著升高(P<0.001)。**结论** T2DM并发DR患者血清CTRP9水平升高可能是糖尿病视网膜微血管病变的代偿反应。
关键词:糖尿病,2型;糖尿病视网膜病;C1q肿瘤坏死因子相关蛋白9

Association between serum CTRP9 levels and diabetic retinopathy in patients with type 2 diabetes mellitus

ZHOU Pengpeng[1,2], LIU Liyan[1], GAO Weiping[2]
[1]Kunshan Chinese Medicine Hospital Affiliated to Nanjing University of Chinese Medicine, Kunshan 215300, China; [2]Nanjing University of Chinese Medicine, Nanjing 210029, China

Abstract: Objective To investigate the relationship between serum C1q tumor necrosis factor-related protein 9 (CTRP9) level and the risk of diabetic retinopathy (DR) in patients with type 2 diabetes mellitus (T2DM). **Methods** A total of 291 patients with T2DM underwent fundus examination, and their serum levels of CTRP9, insulin and adiponectin were measured using enzyme-linked immunosorbent assay. According to results of fundus examination, the patients were divided into DR group and non-DR (NDR) group, and logistic regression was used to analyze the relationship between serum CTRP9 levels and DR in T2DM patients. **Results** Compared with those in NDR group, the patients with DR showed significantly increased serum CTRP9 level (P<0.001) and decreased serum adiponectin level (P<0.001). Pearson correlation analysis showed that in patients with T2DM complicated by DR, serum CTRP9 levels had a significant positive correlation with DR stage (P<0.05) and a negative correlation with serum adiponectin level (P<0.001). Multivariate logistic regression analysis showed that with the increase of serum CTRP9 level, the risk of DR is significantly increased in patients with T2DM. **Conclusion** In patients with T2DM complicated by DR, an increased serum CTRP9 level suggests a compensatory response to DR.
Keywords: diabetes mellitus, type 2; diabetic retinopathy; C1q tumor necrosis factor-related protein 9

糖尿病视网膜病变(DR)是糖尿病常见的微血管并发症之一,是成人视力低下和失明的主要原因[1-3]。补体C1q肿瘤坏死因子相关蛋白9(CTRP9)是一种与脂联素高度同源的脂肪因子[4],具有抗炎,抗氧化,舒张血管的作用[5-9]。此外,它可以增加胰岛素敏感性,降低血糖水平并抑制血管内皮细胞凋亡[10-13]。动物实验研究显示CTRP9对DR具有治疗作用,CTRP9抑制2型糖尿病(T2DM)模型小鼠视网膜炎症因子白介素-1β(IL-1β),肿瘤坏死因子-α(TNF-α),单核细胞趋化蛋白1(MCP-1)和粘附分子的表达,平衡色素上皮衍生因子(PEDF)和血管内皮生长因子(VEGF)的表达,防止T2DM模型小鼠血视网膜屏障(BRB)的破坏和紧密连接蛋白的下调[14]。尽管上述动物实验显示CTRP9在DR的发病过程中发挥着重要作用,但尚缺乏有关CTRP9与DR关联的临床证据。本研究调查了T2DM患者血清CTRP9水平是否与DR有关,结果显示随着血清CTRP9水平的升高,T2DM并发DR的风险显著升高,提示T2DM并发DR患者血清CTRP9水平升高可能是糖尿病视网膜微血管病变的代偿反应。

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作者简介:周鹏鹏,博士研究生,副主任中医师,E-mail: 13584939429@139.com
通信作者:高卫萍,教授,主任中医师,博士生导师,E-mail: Gaoweiping@163.com

1 资料和方法

1.1 研究对象

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泌科门诊就诊且临床生化资料完整的291例T2DM患者。排除标准:(1)1型糖尿病;(2)严重心血管疾病;(3)严重肝损害;(4)结缔组织疾病;(5)恶性肿瘤;(6)急性感染期;(7)妊娠或经期妇女;(8)可能影响眼循环的任何其他眼疾;(9)之前进行玻璃体内注射;(10)影响体重的任何因素,甲状腺功能亢进症,皮质类固醇或避孕药具。本研究是经昆山市中医院伦理委员会审核批准的横断面研究(批准号:KZY2017-06)。

1.2 方法

1.2.1 一般资料收集患者临床基本资料包括:性别、年龄、T2DM病程、高血压病史、收缩压(SBP)、舒张压(DBP)、体质量指数(BMI,BMI=体质量/身高^2)。

1.2.2 生化检测所有患者的血液样本均在禁食过夜后获得。罗氏ROCHE8000全自动生化分析仪检测血脂,包括高密度脂蛋白(HDL-C),低密度脂蛋白(LDL-C),甘油三酸酯(TG),总胆固醇(TC),载脂蛋白A(APOA)和载脂蛋白B(APOB);肾功能,包括血尿素、血肌酐;血糖,血尿酸和C反应蛋白(CRP)。美国伯乐糖化血红蛋白分析仪检测糖化血红蛋白(HbA1c);放免法检测胰岛素;计算胰岛素抵抗指数(HOMA-IR)空腹血糖×空腹胰岛素/22.5

1.2.3 糖尿病视网膜病变程度依据2002年国际分级标准[15]分为:无明显视网膜病变(NDR);轻度非增殖期糖尿病性视网膜病变(NPDR)——仅见微动脉瘤;中度NPDR——有微动脉瘤,但程度轻于重度NPDR;重度NPDR——无PDR表现,但有下列任一表现:(1)任一象限有多于20处的视网膜内出血;(2)超过2个象限内静脉串珠样改变;(3)1个或以上象限有显著的视网膜内微血管异常;增殖期糖尿病性视网膜病变(PDR)——有明显的新生血管形成、视网膜前出血或玻璃体出血。本研究中NDR为NDR组,轻、中、重度NPDR及PDR为DR组。

1.2.4 血清CTRP9、脂联素的测定酶联免疫吸附(ELISA)法测定血清CTRP9、脂联素的水平(BioVendor)。具体操作,按照试剂盒说明进行。CTRP9可检测水平为25~800 pg/mL,脂联素可检测水平为0.1~10 μg/mL,批内及批间变异系数均<10%。

1.3 统计学分析

使用易侃统计软件包(Empower Stats)和R软件进行数据分析。均进行正态性检验,计量资料若服从正态分布用均数±标准差表示,若非正态分布用中位数(上下四分位数)表示。正态分布计量资料进行t检验,非正态分布计量资料进行秩和检验(u检验),计数资料采用率来描述并进行卡方检验(χ^2检验)。两变量之间的相关性采用Pearson相关性分析。采用Logistic回归分析,计算OR值,并计算95%可信区间(95%*CI*)。P<0.05为差异有统计学意义。

2 结果

2.1 研究人群的基线特征

291例T2DM患者中,男性162例(55.64%),女性129例(44.38%),平均年龄58±15岁,平均糖尿病病程9.8±8.0年。其中109例T2DM并发DR,轻、中、重NPDR及PDR所占比例分别为9.17%、42.20%、25.68%、22.94%。NDR组与DR组分别为182例(62.54%)和109例(37.46%)。DR组血清CTRP9水平显著高于NDR组;DR组血清脂联素水平显著低于NDR组;与NDR组相比,DR组糖尿病病程较长;空腹胰岛素水平显著升高;HOMA-IR显著升高;DR组合并高血压的比例较NDR组明显升高;DR组收缩压显著高于NDR组;DR组血肌酐显著高于NDR组; DR组血清尿素显著高于NDR组;DR组CRP显著高于NDR组(表1)。

2.2 血清CTRP9水平与T2DM患者、T2DM并发DR患者临床资料的相关性

血清CTRP9水平与T2DM患者BMI、糖尿病病程、收缩压、空腹血糖、空腹胰岛素、HOMA-IR、血肌酐水平、HDL-C、APOA、CRP呈显著正相关。血清CTRP9水平与T2DM患者血清脂联素呈显著负相关。血清CTRP9水平与T2DM并发DR患者BMI、空腹胰岛素、胰岛素抵抗指数、CRP、DR严重程度呈显著正相关。血清CTRP9水平与T2DM并发DR患者血清脂联素呈显著负相关(表2)。

2.3 T2DM患者血清CTRP9水平与T2DM并发DR的回归分析

以是否有DR为因变量,T2DM患者血清CTRP9水平为自变量,进行单因素Logistic回归分析。T2DM患者血清CTRP9每增加1 pg/mL,发生DR风险增加8%,差异具有统计学意义(OR:1.08,95%*CI*:1.06~1.10,P<0.001)。同时校正年龄、BMI、性别、糖尿病病程、高血压、HbA1c、空腹血糖、空腹胰岛素、胰岛素抵抗指数、血清脂联素、HDL-C、LDL-C、TG、TC、APOA、APOB、血肌酐、血尿素、CRP后,T2DM患者血清CTRP9每增加1 pg/mL,发生DR风险增加13%,差异具有统计学意义(OR:1.13,95%*CI*:1.09~1.18,P<0.001)。

3 讨论

DR是糖尿病性微血管病变中最重要的表现,是糖尿病的严重并发症之一[16-17]。血管内皮功能障碍、BRB破坏和新生血管形成是DR的基本病理变化[18-20]。高血糖、高血脂以及在此基础上引发的炎症反应是导致DR基本病理变化的关键因素[21-23]。CTRP9是2009年新发现的一种脂肪因子,与脂联素具有高度同源性[4, 24]。CTRP9可以激活AMPK,MAPK或其他信号通路促进脂质代谢,改善胰岛素敏感性,降低血糖,减轻炎症反

表1 2型糖尿病患者的基线资料

Tab.1 Clinical and biochemical data of type 2 diabetic patients with and without DR

Variable	NDR (*n*=182)	DR (*n*=109)	*T* value (vswvalue, χ^2 value)	*P*
Gender (male/female)	112/70	50/59	6.78	0.009
Age (year)	56±16	60±13	-2.27	0.024
History of hypertension	85 (46.70%)	75 (68.81%)	13.45	<0.001
SBP (mmHg)	135.2±18.6	147.6±23.5	-4.98	<0.001
DBP (mmHg)	81.1±11.8	80.6±14.1	0.36	0.719
Duration of T2DM	6.00 (1.00-10.00)	13.00 (10.00-20.00)	-6.94	<0.001
BMI (kg/m^2)	26.0±3.6	25.1±3.0	2.03	0.030
HbA1C (%)	9.45 (7.80-11.12)	8.80 (7.60-11.30)	-1.99	0.926
FBG (mmol/L)	8.35 (7.23-9.47)	8.50 (7.30-10.40)	-1.53	0.250
Insulin (μU/mL)	8.30 (7.10-9.40)	11.40 (9.80-13.80)	-10.87	<0.001
HOMA-IR	3.10 (2.40-3.90)	4.30 (3.50-5.60)	-7.95	<0.001
Serum urea (mmol/L)	5.28 (4.29-6.75)	6.55 (5.03-11.60)	-1.79	<0.001
Scr (μmol/L)	73.08 (65.02-87.21)	86.80 (73.00-129.50)	-5.79	<0.001
UA (μmol/L)	348.5 (304.0-431.00)	401.0 (327.0-481.0)	-2.11	0.024
TG (mmol/L)	1.55 (1.05-2.59)	1.85 (0.96-2.55)	1.43	0.857
TC (mmol/L)	4.75 (3.90-5.60)	4.90 (3.90-6.27)	-1.90	0.075
HDL-C (mmol/L)	0.94 (0.81-1.12)	1.01 (0.83-1.17)	-1.38	0.110
LDL-C (mmol/L)	3.14±0.92	3.32±1.12	-1.48	0.139
APOA(g/L)	1.13 (0.98-1.26)	1.12 (1.01-1.28)	-0.58	0.416
APOB(g/L)	0.94 (0.74-1.10)	0.94 (0.73-1.24)	-0.81	0.648
CRP (mg/dL)	0.58 (0.22-1.54)	1.13 (0.58-1.99)	-0.40	0.003
Adiponectin (μg/mL)	7.25 (5.95-8.68)	5.95 (5.04-6.79)	8.15	<0.001
CTRP9 (pg/mL)	122.3 (110.8-134.0)	153.5 (140.0-161.0)	-12.27	<0.001

Note: T2DM: Type 2 diabetes; DR: Diabetic retinopathy; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment for insulin resistance; SBP: Systolic blood pressure; DBP: Diastolic blood Pressure; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; UA: uric acid; BMI: Body mass index; Scr: Serum creatinine; UA: uric acid; APOA: Apolipoprotein A; APOB: Apolipoprotein B; CRP: C-reactive protein; CTRP9: C1q tumour necrosis factor-related protein 9.

应，保护血管。Wong等[4]研究显示CTRP9通过AMPK，Akt及MAPK信号通路降低ob/ob肥胖小鼠血清胰岛素及葡萄糖水平。Jung等[25]研究显示CTRP9通过AMPK信号通路阻碍炎症因子TNF-α诱导的NF-κB活化，并抑制血管内皮细胞中黏附分子和趋化因子的表达，减轻血管炎症。

本研究显示，与NDR组比较，DR组T2DM患者血清CTRP9、CRP、HOMA-IR显著升高，血清脂联素显著降低。随着血清CTRP9水平的升高，T2DM并发DR的风险显著升高，且血清CTRP9水平与DR严重程度、CRP、HOMA-IR及BMI呈正相关，与血清脂联素水平呈负相关。既往有多项研究显示，T2DM并发DR患者较未并发DR患者血清CRP、HOMA-IR显著升高，血清脂联素显著降低[26-28]，与本研究结果一致。

血液中的CTRP9主要由脂肪组织分泌，CTRP9蛋白在ob/ob肥胖小鼠脂肪组织、外周血中表达水平上调[4]。研究发现，T2DM患者血清CTRP9水平与BMI呈正相关[29]，肥胖患者肥胖外科手术治疗后CTRP9水平降低[30]。本研究也显示T2DM患者（NDR组和DR组）血清CTRP9水平与BMI呈正相关。这些研究结果提示血清CTRP9水平与机体肥胖状态有关。CTRP9对糖代谢和胰岛素敏感性的有利作用已被证实，流行病学调查研究显示血清CTRP9水平与糖代谢参数呈正相关。Jung、Moradi等[29]研究显示T2DM患者血清CTRP9水平与HOMA-IR呈正相关。Jia等[31]研究显示新诊断的T2DM患者及糖耐量异常患者血清CTRP9水平较糖耐量正常受试者显著升高，且血清CTRP9水平与HOMA-IR呈正相关。脂联素具有增加胰岛素敏感性，抗炎，抗新生血管化等作用，并与CTRP9[32]形成异源二聚体，T2DM患者血清CTRP9水平与血清脂联素呈负相关，提示CTRP9水平的升高可能是脂联素水平降低的代偿反应[33]。体内、外实验研究证实CTRP9对血

表2 血清CTRP9浓度与临床特征的相关性

Tab.2 Correlation between serum CTRP9 concentration and clinical parameters

CTRP9	Variable	T2DM (*n*=291)		DR (*n*=109)	
		r	*P*	*r*	*P*
	Age (years)	0.06	0.303	0.14	0.136
	BMI (kg/m^2)	0.25	<0.001	0.39	<0.001
	Duration of T2DM	0.25	<0.001	0.07	0.422
	SBP (mmHg)	0.17	0.004	0.10	0.304
	DBP (mmHg)	-0.02	0.792	-0.03	0.765
	HbA1C (%)	0.04	0.591	-0.12	0.223
	FBG (mmol/L)	0.13	0.031	0.02	0.804
	Insulin (μU/mL)	0.34	<0.001	0.33	<0.001
	HOMA-IR	0.32	<0.001	0.22	0.019
	Serum urea (mmol/L)	0.11	0.061	0.13	0.166
	Scr (μmol/L)	0.13	0.027	0.16	0.095
	UA (μmol/L)	-0.02	0.666	-0.15	0.121
	TG (mmol/L)	0.06	0.289	0.07	0.479
	TC (mmol/L)	0.09	0.143	-0.11	0.233
	HDL-C (mmol/L)	0.16	0.007	-0.05	0.638
	LDL-C (mmol/L)	0.05	0.358	-0.08	0.390
	APOA (g/L)	0.13	0.027	0.01	0.970
	APOB (g/L)	0.10	0.118	0.01	0.979
	CP (mg/dL)	0.21	<0.001	0.39	<0.001
	Adiponectin (μg/mL)	-0.27	<0.001	-0.23	0.017
	Stage of DR	-	-	0.48	<0.001

T2DM: Type 2 diabetes; DR: Diabetic retinopathy; HbA1c: Glycosylated hemoglobin; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment for insulin resistance; SBP: Systolic blood pressure; DBP: Diastolic blood Pressure; TC: Total cholesterol; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; UA: uric acid; BMI: Body mass index; Scr: Serum creatinine; UA: Uric acid; APOA: Apolipoprotein A; APOB: Apolipoprotein B; CRP: C-reactive protein; CTRP9: C1q tumour necrosis factor-related protein.

管内皮细胞具有保护，T2DM患者血清CTRP9水平与脉搏波速度呈负相关，脉搏波速度是反应动脉粥样硬化的指标[29]。Moradi 等[33]研究显示T2DM患者血清CTRP9水平与血清粘附分子、IL-6及TNF-α水平呈正相关。鉴于CTRP9具有改善胰岛素敏感性、抗炎和保护血管内皮的作用，本研究T2DM并发DR患者血清CTRP9水平升高可能是机体对胰岛素抵抗、微血管炎症损伤的代偿反应[26-28]。

此外，通过查阅文献，至目前为止，我们只发现一项关于血清CTRP9水平与DR关系的研究，王欣荣等研究显示随着血清CTRP9 水平降低，DR 患病风险显著增加，与本研究的结果相反。导致这些差异结果的原因尚不清楚，可能是由于研究对象的纳排标准不同所致。且王欣荣等的研究，其研究对象样本例数较少，其中无DR的T2DM患者（*n*=50）及DR患者（*n*=60）[34]。

本研究为单中心、小样本、横断面研究，尚需多中心、大样本和前瞻性队列研究加以证实。此外，本研究纳入的T2DM患者，未排除降血糖、降血压及降血脂药物对CTRP9的影响，这些药物是否对CTRP9产生影响目前尚不清楚。

综上所述，本研究发现血清CTRP9浓度与T2DM并发DR呈显著正相关，提示CTRP9可能是糖尿病视网膜微血管病变的代偿反应，有必要进一步研究CTRP9在DR 中的分子作用机制。

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