

· 临床研究 ·

糖尿病视网膜膜病变患者血清补体因子含量变化

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【摘要】目的 检测糖尿病视网膜膜病变(DR)患者血清补体因子 C3 和 C4 的含量变化,探讨其在 DR 发生和发展中的作用。**方法** 采用病例对照研究设计,选取 2017 年 12 月至 2018 年 12 月在哈尔滨医科大学附属第一医院确诊的 DR 患者 195 例作为 DR 组,纳入 2 型糖尿病患者 150 例作为糖尿病组,同期收集 281 例单纯年龄相关性白内障或斜视患者作为对照组。采集受检者晨起空腹静脉血并分离血清。采用免疫散射比浊法测定血清中 C3、C4 的质量浓度。采用速率法测定谷丙转氨酶(ALT)、谷草转氨酶(AST)的含量;采用酶法测定总胆固醇、三酰甘油的含量。采用 Pearson 线性相关分析法评估各组血清补体因子 C3 和 C4 与各临床参数的相关性,采用逐步回归分析法评估补体因子 C3 和 C4 水平的影响因素。**结果** 糖尿病组血清中 C3 质量浓度为(1 154.0±177.4)mg/L,明显高于 DR 组的(1 077.3±177.0)mg/L 和对照组的(1 072.0±184.3)mg/L,差异均有统计学意义(均 $P < 0.05$);DR 组血清补体因子 C4 质量浓度为(287.5±83.5)mg/L,明显高于糖尿病组的(257.5±70.1)mg/L 和对照组的(263.7±77.2)mg/L,差异均有统计学意义(均 $P < 0.05$)。相关性分析结果显示,在糖尿病及 DR 组中补体因子 C3 的表达水平与总胆固醇及三酰甘油均呈弱正相关(糖尿病组: $r = 0.250$ 、 0.205 ,均 $P < 0.05$;DR 组: $r = 0.308$ 、 0.213 ,均 $P < 0.01$);在 DR 组中补体因子 C4 的表达水平与总胆固醇及三酰甘油均呈弱正相关($r = 0.235$, $P = 0.002$; $r = 0.247$, $P = 0.001$)。多元回归分析表明总胆固醇及三酰甘油是 DR 组血清 C3、C4 表达的影响因素。**结论** 补体因子可能参与了 DR 的病理进程,DR 患者血清补体因子 C3 和 C4 受血清总胆固醇和三酰甘油的影响。

【关键词】 糖尿病视网膜膜病变; 补体因子 C3; 补体因子 C4**基金项目:** 国家自然科学基金项目(81500711); 黑龙江省自然科学基金项目(QC2015094)

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【Abstract】Objective To detect the changes of serum complement factors C3 and C4 in diabetic retinopathy (DR) patients, and to explore their role in the occurrence and development of DR. **Methods** A cases-controlled study was carried out. Total of 195 patients with DR diagnosed in the First Affiliated Hospital of Harbin Medical University from December 2017 to December 2018 were selected as the DR group, 150 patients with type 2 diabetes were included as the diabetes group, and 281 simple age-related cataract or strabismus patients were collected at the same time and served as control group. Fasting venous blood was collected and serum was isolated. The concentration of C3 and C4 in serum was determined by immunoturbidimetry. The contents of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by rate method, and the contents of total cholesterol and triglyceride were determined by enzyme method. Pearson linear correlation analysis was used to evaluate the correlation between serum complement factors and clinical parameters. Stepwise regression analysis was used to evaluate the influencing factors of complement factor C3 and C4 expression. This study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethical Committee Review Board of the First Affiliated Hospital of Harbin Medical University (No. 2016-81500711). **Results** The concentration of serum complement factor C3 in the diabetes group was (1 154.0±177.4)mg/L, which was significantly higher than (1 077.3±177.0)mg/L in the

DR group and $(1\,072.0 \pm 184.3)$ mg/L in the control group, the differences were statistically significant (all at $P < 0.05$); The concentration of serum complement factor C4 in the DR group was (287.5 ± 83.5) mg/L, which was significantly higher than (257.5 ± 70.1) mg/L in the diabetes group and (263.7 ± 77.2) mg/L in the control group, the differences were statistically significant (all at $P < 0.05$). The correlation analysis results showed that the expression level of complement factor C3 was weakly positively correlated with total cholesterol and triglyceride in the diabetes and DR groups (diabetes group: $r = 0.250, P < 0.05$; $r = 0.205, P < 0.05$. DR group: $r = 0.308, P < 0.01$; $r = 0.213, P < 0.01$); The expression level of complement factor C4 was weakly positively correlated with total cholesterol and triglyceride in the DR group ($r = 0.235, P = 0.002$; $r = 0.247, P = 0.001$). Multiple regression analysis showed that total cholesterol and triglyceride were the influencing factors of serum C3 and C4 expression in the DR group.

Conclusions Complement factors may participate in the pathological process of DR and serum complement factors C3 and C4 are affected by serum total cholesterol and triglyceride in DR patients.

[Key words] Diabetic retinopathy; Complement factor C3; Complement factor C4

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近年来,糖尿病患者迅速增加,2010 年的统计数据表明中国 20 岁以上糖尿病患者已超过 9 200 万^[1]。糖尿病视网膜病变(diabetic retinopathy, DR)是糖尿病常见眼部并发症,其发病率逐年升高,是目前中国工作年龄人群首位致盲眼病^[2-3]。DR 影响人群广泛,治疗预后差,使其成为目前眼科研究的重点和热点。DR 发病机制复杂,长期慢性高血糖是其发病的基础,高血压、高血脂等是其发病的危险因素,但 DR 的确切机制尚不十分清楚^[4-6]。最新研究表明,DR 病变进程中出现白细胞淤滞和炎症介质上调等现象,推测补体系统所介导的炎症反应参与了 DR 的发生和发展^[7]。本课题组前期实验已证明补体通路调控基因与 DR 发病风险相关,但补体通路中相关因子的表达水平与 DR 是否相关尚未明确^[8]。本研究通过检测糖尿病及 DR 患者血清中补体因子 C3、C4 的表达,以进一步探索血清补体因子含量变化与 DR 的关系及其意义。

1 资料与方法

1.1 一般资料

采用病例对照研究设计,选取 2017 年 12 月至 2018 年 12 月在哈尔滨医科大学附属第一医院眼科分院经荧光素眼底血管造影(fundus fluorescein angiography, FFA)确诊的 DR 患者 195 例作为 DR 组,其中男 108 例,女 87 例;平均年龄 (55.53 ± 10.92) 岁。同期纳入在内分泌科收治的 2 型糖尿病患者 150 例作为糖尿病组,其中男 93 例,女 57 例;平均年龄 (52.01 ± 10.11) 岁。依据 1999 年糖尿病诊断标准^[9]进行诊断。糖尿病组纳入标准:糖尿病病程大于 5 年且经 FFA 检查无视网膜微血管病变者。入院时询问胰岛素治疗情况,其中 DR 患者 49.2%、糖尿病患者 28.8%有

胰岛素治疗史。另选 281 例年龄相关性白内障或斜视患者作为对照组,其中男 149 例,女 132 例;平均年龄 (57.0 ± 15.0) 岁,并排除糖尿病病史、急慢性感染性疾病、肝肾功能不全、肿瘤及其他炎症性疾病。各组纳入患者均无高血压和高血脂。对照组、糖尿病组和 DR 组年龄、糖尿病病程、空腹血糖、糖化血红蛋白(hemoglobin A1C, HbA1c)、体质量指数(body mass index, BMI)比较,差异均有统计学意义(均 $P < 0.05$);各组患者中收缩压和舒张压总体比较,差异均有统计学意义($F = 6.411, P = 0.002$; $F = 18.810, P < 0.001$)。其中糖尿病组患者收缩压和舒张压均明显高于 DR 组和对照组,差异均有统计学意义(均 $P < 0.05$)。各组性别构成比比较,差异无统计学意义($P > 0.05$) (表 1)。本研究遵循赫尔辛基宣言,本研究方案经哈尔滨医科大学附属第一医院伦理委员会审核批准(批文号:2016-81500711)。所有受检者均自愿参加并签署知情同意书。

1.2 方法

1.2.1 标本采集 受检者禁食 12 h,采取次日晨起空腹肘静脉血 5 ml,离心取上清液, $-20\text{ }^{\circ}\text{C}$ 保存。收集受检者性别、年龄、身高、BMI、血压、现病史、既往史等信息。

1.2.2 眼科一般检查 所有受检者均在暗室接受详细的视力、眼前节及眼底检查,包括应用有 300 lx 以上照明的 EDTRS 视力表(江苏巨光光电科技有限公司)检查视力;裂隙灯显微镜(YZ-5 型,苏州六六公司)检查眼前节,包括角膜透明度、前房深度、瞳孔大小及对光反应、虹膜纹理及晶状体混浊程度;检眼镜(YZ-11, 苏州六六视觉科技股份有限公司)检查患者眼底有或无视网膜微血管并发症及其他眼底疾患。检查由本组副主任医师及 2 名研究生共同完成。所有 DR 患者均

表 1 各组基线资料比较
Table 1 Comparison of the demography among different groups

组别	例数	年龄 (mean±SD, 岁) [*]	性别构成比 (男/女, n) [#]	糖尿病病程 (mean±SD, 岁) [*]	空腹血糖 (mean±SD, mmol/L) [*]	HbA1c (mean±SD, %) [*]	BMI (mean±SD, kg/m ²) [*]	收缩压 (mean±SD, mmHg) [*]	舒张压 (mean±SD, mmHg) [*]
糖尿病组	150	52.01±10.11	93/ 57	11.2±5.7	8.55±3.18	8.12±1.45	27.02±4.73	132.39±19.99	74.65±14.06
DR 组	195	55.53±10.92	108/ 87	12.9±7.1 ^a	9.28±3.92	8.29±1.41	23.53±5.84 ^a	130.88±20.14 ^a	78.05±13.45 ^a
对照组	281	57.02±15.00 ^a	149/132	-	6.32±0.89 ^a	6.47±1.23 ^a	26.12±4.51	138.09±20.53 ^a	83.41±11.38 ^a
t/χ ² 值		7.592	3.228	2.398	74.520	131.700	24.110	6.411	18.810
P 值		0.001	0.199	0.017	<0.001	<0.001	<0.001	0.002	<0.001

注:(^{*}:单因素方差分析;[#]:χ² 检验)与糖尿病组比较,^aP<0.05 HbA1c:糖化血红蛋白;BMI:体质量指数;DR:糖尿病视网膜病变(1 mmHg=0.133 kPa)

Note:(^{*}:One way ANOVA;[#]:χ² test) Compared with the diabetes group,^aP<0.05 HbA1c:hemoglobin A1C;BMI:body mass index;DR:diabetes retinopathy(1 mmHg=0.133 kPa)

行 FFA(HRA 共焦激光眼底扫描系统,德国海德堡公司)检查,此检查由眼科检查室副主任医师独立完成。

1.2.3 血液生物化学指标检查 检验科按照补体 C3、C4 试剂盒(德国西门子公司)说明书采用免疫散射比浊法测定血清 C3、C4 的质量浓度;采用 AU680 Beckman Coulter K. K 全自动生化分析仪(美国 Beckman-Coulter 公司)并按照谷丙转氨酶(alanine aminotransferase, ALT)、谷草转氨酶(aspartate transaminase, AST)、总胆固醇、三酰甘油试剂盒(上海纪宁实业有限公司)说明书采用速率法测定 ALT、AST 含量,酶法测定总胆固醇、三酰甘油的含量。

1.3 统计学方法

采用 SPSS 20.0 软件进行统计分析。本研究中计量资料经 Shapiro-Wilk 检验证实接近正态分布,以 mean±SD 表示。糖尿病组、DR 组和对照组受检者 BMI、收缩压、舒张压、C3、C4、AST、ALT、总胆固醇、三酰甘油含量总体差异比较采用单因素方差分析,组间多重比较采用 LSD-t 检验。糖尿病组和 DR 组补体因子 C3、C4 水平与多种临床参数(收缩压、舒张压、

ALT、AST、总胆固醇、三酰甘油)相关性分析采用 Pearson 线性相关分析,采用逐步回归分析法评估补体 C3、C4 水平的影响因素。P<0.05 为差异有统计学意义。

2 结果

2.1 各组血清生物化学指标及补体因子 C3、C4 表达比较

各组血清补体因子 C3、C4 质量浓度总体比较,差异均有统计学意义(F=11.269、7.803,均 P<0.001)。糖尿病组血清 C3 质量浓度明显高于 DR 组和对照组,差异有统计学意义(均 P<0.001)。DR 组血清 C4 质量浓度明显高于糖尿病和对照组,差异均有统计学意义(均 P<0.01)(表 2)。

各组血清 ALT 和三酰甘油总体比较,差异均有统计学意义(F=4.454, P=0.012; F=12.232, P<0.001)。糖尿病组血清 ALT 质量浓度明显高于 DR 组和对照组,对照组血清三酰甘油质量浓度明显低于糖尿病组和 DR 组,差异均有统计学意义(均 P<0.05)(表 2)。

表 2 各组患者各临床参数及补体因子水平比较(mean±SD)
Table 2 Comparison of demographic and laboratory data among the three groups (mean±SD)

组别	样本量 (例)	C3 (mg/L)	C4 (mg/L)	ALT (U/L)	AST (U/L)	总胆固醇 (mmol/L)	三酰甘油 (mmol/L)
糖尿病组	150	1154.0±177.4	257.5±70.1	28.15±23.24	23.32±13.48	5.15±1.05	2.31±1.65
DR 组	195	1077.3±177.0 ^a	287.5±83.5 ^a	21.49±23.75 ^a	22.18±25.14	5.24±1.18	2.17±1.64
对照组	281	1072.0±184.3 ^a	263.7±77.2 ^b	22.28±19.38 ^a	22.64±10.03	5.05±1.08	1.67±0.89 ^{ab}
F 值		11.269	7.803	4.454	0.182	1.459	12.232
P 值		<0.001	<0.001	0.012	0.833	0.233	<0.001

注:与糖尿病组比较,^aP<0.05;与 DR 组比较,^bP<0.05(单因素方差分析,LSD-t 检验) 1 mmHg=0.133 kPa;DR:糖尿病视网膜病变;ALT:谷丙转氨酶;AST:谷草转氨酶

Note:Compared with the diabetes group,^aP<0.05;compared with the DR group,^bP<0.05(One way ANOVA, LSD-t test) 1 mmHg=0.133 kPa DR:diabetic retinopathy;ALT:alanine aminotransferase;AST:aspartate transaminase

2.2 补体因子 C3、C4 水平与各血液生物化学指标相关性分析

Pearson 线性相关性分析结果提示,糖尿病组血清 C3 质量浓度与收缩压、舒张压、总胆固醇及三酰甘油均呈弱正相关 ($r = 0.181, P = 0.027; r = 0.204, P = 0.012; r = 0.250, P = 0.003; r = 0.205, P = 0.016$), 与 ALT 及 AST 均无明显相关 ($r = 0.137, P = 0.107; r = 0.146, P = 0.086$); 血清 C4 质量浓度与收缩压、舒张压、ALT、AST、总胆固醇及三酰甘油均无明显相关 ($r = 0.096, P = 0.242; r = 0.025, P = 0.761; r = -0.031, P = 0.714; r = 0.003, P = 0.973; r = 0.119, P = 0.164; r =$

$0.054, P = 0.532$) (图 1)。

DR 组血清 C3 质量浓度与总胆固醇及三酰甘油均呈弱正相关 ($r = 0.308, P < 0.001; r = 0.213, P = 0.005$), 与收缩压、舒张压、ALT、AST 均无明显相关 ($r = -0.006, P = 0.935; r = 0.048, P = 0.507; r = -0.030, P = 0.688; r = -0.072, P = 0.330$); 血清 C4 浓度与总胆固醇及三酰甘油均呈弱正相关 ($r = 0.235, P = 0.002; r = 0.247, P = 0.001$), 与收缩压、舒张压、ALT、AST 均无明显相关 ($r = -0.002, P = 0.98; r = 0.002, P = 0.975; r = -0.132, P = 0.073; r = -0.092, P = 0.210$) (图 2)。

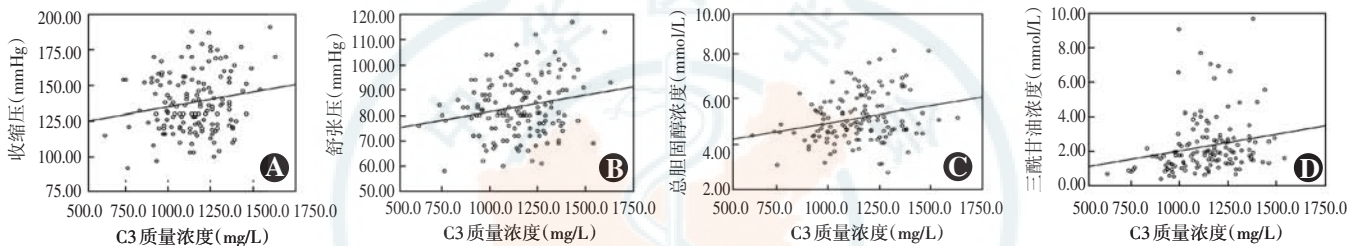


图 1 糖尿病患者血清 C3 水平与各临床参数的相关性 (Pearson 线性相关分析, $n = 150$) A: 血清 C3 质量浓度与收缩压呈弱正相关 ($r = 0.181, P = 0.027$) B: 血清 C3 质量浓度与舒张压呈弱正相关 ($r = 0.204, P = 0.012$) C: 血清 C3 质量浓度与总胆固醇浓度呈弱正相关 ($r = 0.250, P = 0.003$) D: 血清 C3 质量浓度与三酰甘油浓度呈弱正相关 ($r = 0.205, P = 0.016$) (1 mmHg = 0.133 kPa)

Figure 1 Correlation between serum C3 level and clinical parameters in the diabetes group (Pearson linear correlation analysis, $n = 150$) A: The serum concentration of C3 was weakly positively correlated with systolic blood pressure ($r = 0.181, P = 0.027$) B: The serum concentration of C3 was weakly positively correlated with diastolic blood pressure ($r = 0.204, P = 0.012$) C: The serum concentration of C3 was weakly positively correlated with total cholesterol ($r = 0.250, P = 0.003$) D: The serum concentration of C3 was weakly positively correlated with triglyceride ($r = 0.205, P = 0.016$) (1 mmHg = 0.133 kPa)

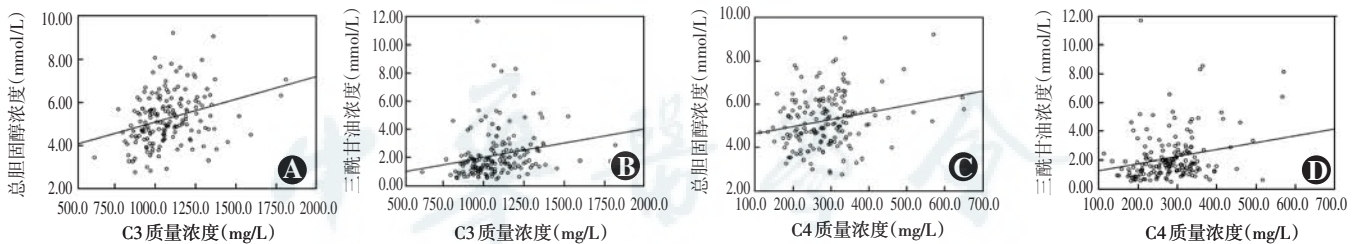


图 2 DR 组患者血清 C3 和 C4 水平与总胆固醇和三酰甘油的相关性 (Pearson 线性相关分析, $n = 195$) A: 血清 C3 质量浓度与总胆固醇浓度呈弱正相关 ($r = 0.308, P < 0.001$) B: 血清 C3 质量浓度与三酰甘油浓度呈弱正相关 ($r = 0.213, P = 0.005$) C: 血清 C4 质量浓度与总胆固醇浓度呈弱正相关 ($r = 0.235, P = 0.002$) D: 血清 C4 质量浓度与三酰甘油浓度呈弱正相关 ($r = 0.247, P = 0.001$)

Figure 2 Correlation of serum C3 and C4 levels with total cholesterol and triglyceride in the DR group (Pearson linear correlation analysis, $n = 195$) A: The serum concentration of C3 was weakly positively correlated with total cholesterol ($r = 0.308, P < 0.001$) B: The serum concentration of C3 was weakly positively correlated with triglyceride ($r = 0.213, P = 0.005$) C: The serum concentration of C4 was weakly positively correlated with total cholesterol ($r = 0.235, P = 0.002$) D: The serum concentration of C4 was weakly positively correlated with triglyceride ($r = 0.247, P = 0.001$)

2.3 DR 组患者补体因子 C3、C4 水平相关因素分析

分别以 DR 组补体因子 C3、C4 水平为因变量, 年龄、性别、BMI、收缩压、舒张压、ALT、AST、总胆固醇和三酰甘油为自变量, 进行逐步多元线性回归分析, 建立回归方程: $C3 = 85.849 + 4.194 \times$ 总胆固醇; $C4 = 20.17 +$

$0.947 \times TG + 1.254 \times$ 总胆固醇。结果显示总胆固醇 ($\beta = 4.194, P < 0.001$) 是 DR 组补体因子 C3 的影响因素, 三酰甘油 ($\beta = 0.947, P = 0.021$) 和总胆固醇 ($\beta = 1.254, P = 0.026$) 是 DR 组补体因子 C4 的影响因素 (表 3)。

表 3 DR 患者补体因子 C3、C4 水平的相关因素分析
Table 2 Stepwise multivariate regression analysis of C3 and C4 levels and related factors in the DR group

模型变量		非标准化相关系数 (β)	<i>t</i> 值	<i>P</i> 值
C3	总胆固醇 (mmol/L)	4.194	4.10	<0.001
C4	三酰甘油 (mmol/L)	0.947	2.33	0.021
	总胆固醇 (mmol/L)	1.254	2.24	0.026

注:(逐步回归分析法)

Note:(Stepwise regression analysis)

3 讨论

DR 是一种多因素参与的致盲眼病,最新研究表明慢性炎症反应在 DR 的病理机制中发挥重要作用,炎症与免疫调节因素贯穿 DR 发生和发展的整个过程^[10]。补体系统是人类先天性免疫防御系统的一部分,广泛参与机体微生物防御反应及免疫调节,介导免疫病理的损伤性反应,是体内具有重要生物学作用的效应体系。补体激活途径包括经典途径、alternative 途径(又称旁路途径)以及 Lectin 途径^[11-12]。生理情况下,补体系统的激活与抑制存在一种平衡状态,这种平衡一旦被某种因素打破则可能形成过多的炎症介质或诱发过度的炎症级联反应,进而对机体产生有害影响^[13]。

C3、C4 是补体因子中的核心成员,其活化在炎症调节中起着关键作用。研究显示,补体因子 C3 在糖尿病患者血清中呈高水平表达,组织中亦有补体及补体激活物的沉积,提示补体系统可能参与糖尿病病的病理进程^[14-17]。研究发现,DR 患者眼内组织脉络膜血管中有明显的 C3 和膜攻击复合物(membrane attack complex, MAC)的沉积^[18]。与此同时,补体因子及其复合物在眼内组织中的表达也被后续研究证实,如 DR 患者视网膜内衰变加速因子(decay-accelerating factor, DAF)和 CD59 的表达量明显下降,证明调节系统的失衡可能是补体过度激活致病的主要原因^[17]。另有一项研究结果显示,与对照组相比, PDR 患者玻璃体腔液补体因子 B(complement factor B, CFB)、C3、C4b 和 C9 均有明显升高,并由此认为补体系统的激活在 DR 病程中起到至关重要的作用^[18]。鉴于补体调控因子在眼内结构中的普遍表达,动物研究中所得到的关于补体系统与 DR 发生的生物学关联,以及我们前期基因学研究中所得到的关于补体基因与 DR 的相

关性证据^[8],推测 DR 的发生和发展应与某些补体重要的调控因子存在关联。本研究结果显示补体因子 C4 在 DR 患者血清中呈现高表达,推测 DR 病理进程中有补体所诱发的炎症反应参与;与之相反, C3 在 DR 患者血清中呈低表达,这可能是补体级联反应的过度激活使得 C3 被大量消耗,导致补体平衡被打破,进而诱发病理过程。

Srinivasan 等^[19]研究发现血脂控制不良、脂质类型异常是 DR 发生和发展的危险因素。血管内皮功能障碍是关键的病理改变,其中高脂质水平通过降低一氧化氮的生物利用度而引起内皮功能障碍^[20]。高脂血症可能通过介导内皮功能障碍和破坏视网膜内屏障导致血脂和脂蛋白渗出,继而引起 DR^[21-22]。酰化刺激蛋白(acylation stimulating protein, ASP)为 C3 的裂解产物,是一种旁分泌代谢因子,刺激人体脂肪组织对葡萄糖的摄取和脂肪的储存^[23-25]。研究表明,血清 C3 水平与内脏脂肪组织、皮下脂肪组织及总脂肪组织密切相关^[26]。本研究也证明 DR 患者血清 C3 和 C4 质量浓度与总胆固醇及三酰甘油含量均呈明显相关。

本研究也存在一定的局限性:首先,本研究样本量相对较小,且各因素之间相关系数值较小,由于该研究是基于医院患者人群,且 DR 及糖尿病是典型的多因素疾病,对此影响因素的探讨仍需扩大样本量进一步研究;其次,患者基线及治疗情况差异大,对照组亦包含白内障、斜视等人群,虽然在较大程度上排除了炎症的参与,但这些混杂因素仍可能影响对结果的解读。因此,在今后的研究中,需要扩大样本量,对补体因子及其影响因素进行全面分析和探索。

本研究结果表明,DR 患者的血清补体因子 C3、C4 水平与对照组间存在差异性表达,推测补体调节可能参与 DR 病变进程。DR 患者补体因子 C3 和 C4 受血清总胆固醇和三酰甘油影响,为 DR 的机制研究及临床诊治提供了新思路和新靶点。

利益冲突 所有作者均声明不存在利益冲突

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