

2型糖尿病并发视网膜病变患者血清脂联素和超敏C-反应蛋白浓度的变化

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Changes of the concentration of serum adiponectin and high sensitivity C-reactive protein in type 2 diabetes mellitus patients with retinopathy

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Abstract

• **AIM:** To explore the changes of the concentration of serum adiponectin (APN) and high sensitivity C-reactive protein (hs-CRP) in type 2 diabetes mellitus patients with diabetic retinopathy (DR).

• **METHODS:** The concentration of serum APN and hs-CRP in 49 no-DR (NDR) patients were determined by ELISA and ratenephelometry and compared with those in 46 no-PDR (NPDR) patients, 41 proliferative diabetic retinopathy (PDR) patients and 45 controls. Data were evaluated using analysis of SPSS version 11.0. Results were expressed as means standard deviation of the mean. Statistical comparisons were performed by One-way analysis of variance and the means compared each other using q test.

• **RESULTS:** The serum APN and hs-CRP in NDR patients were 8.76 ± 3.61 mg/L, 3.12 ± 1.24 mg/L; in NPDR patients were 6.22 ± 2.53 mg/L, 4.89 ± 1.66 mg/L; in PDR patients

were 3.98 ± 1.86 mg/L, 6.95 ± 2.59 mg/L and in controls were 13.55 ± 5.87 mg/L, 2.01 ± 0.85 mg/L. There were significant differences in serum APN and hs-CRP between controls and NDR patients, NDR and NPDR patients NPDR and PDR patients ($q = 5.4401, P = 0.000; q = 2.4367, P = 0.0017. q = 3.1535, P = 0.002; q = 2.0572, P = 0.003. q = 4.8756, P = 0.000; q = 2.6184, P = 0.001$). There was significant negative correlation between serum APN and hs-CRP in DR patients ($r = -0.643, P < 0.01$).

• **CONCLUSION:** There is significant negative correlation between serum APN and hs-CRP in DR patients. The serum APN concentration decreases while the serum hs-CRP concentration increases, which may contribute to the development of DR.

• **KEYWORDS:** diabetic retinopathy; adiponectin; high sensitivity C-reactive protein

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摘要

目的: 探讨2型糖尿病并发视网膜病变(diabetic retinopathy, DR)患者血清脂联素和超敏C-反应蛋白(high sensitivity C-reactive protein, hs-CRP)浓度的变化。

方法: 病例对照研究。采用酶联免疫吸附法和速率散射比浊法检测49例非糖尿病视网膜病变(NDR)的糖尿病患者, 46例非增生性糖尿病视网膜病变(NPDR)组患者, 41例增生性糖尿病视网膜病变(PDR)组患者以及45例对照组受检者血清脂联素和超敏C-反应蛋白(hs-CRP)浓度的变化, 采用单因素设计的定量资料的方差分析, 多个均数之间两两比较采用 q 检验, 相关分析采用直线相关分析。

结果: NDR组患者血清脂联素浓度 8.76 ± 3.61 mg/L, hs-CRP浓度 3.12 ± 1.24 mg/L; NPDR组患者血清脂联素浓度 6.22 ± 2.53 mg/L, hs-CRP浓度 4.89 ± 1.66 mg/L; PDR组患者血清脂联素浓度 3.98 ± 1.86 mg/L, hs-CRP浓度 6.95 ± 2.59 mg/L; 对照组血清脂联素浓度 13.55 ± 5.87 mg/L, hs-CRP浓度 2.01 ± 0.85 mg/L。正常对照组与NDR组、NDR组与NPDR组、NPDR组与PDR组的血清脂联素比较, 差异有统计学意义($q = 5.4401, P = 0.000; q = 3.1535, P = 0.002; q = 4.8756, P = 0.000$)。正常对照组与NDR组、NDR组与NPDR组、NPDR组与PDR组血清hs-CRP浓度比较, 差异具有统计学意义($q = 2.4367, P = 0.0017; q = 2.0572, P =$

0.003; $q = 2.6184, P = 0.001$)。DR患者血清hs-CRP与血清脂联素水平呈负相关($r = -0.643, P < 0.01$)。

结论:DR患者血清脂联素浓度水平与血清hs-CRP浓度水平存在显著负相关,血清脂联素浓度水平下降,伴随着血清hs-CRP浓度水平的升高,且与糖尿病视网膜病变的严重程度相关。

关键词:糖尿病视网膜病变;脂联素;超敏C-反应蛋白

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0 引言

糖尿病视网膜病变(diabetic retinopathy, DR)是糖尿病最常见的微血管并发症之一,是成人首位致盲眼病,至今其发病机制尚未完全阐明。炎症反应与糖尿病视网膜病变的关系成了近年研究所关注的热点。超敏C-反应蛋白(high sensitivity C-reactive protein, hs-CRP)是人体最敏感的非特异性炎症反应标志物之一,国外研究发现hs-CRP与糖尿病微血管病变的发生有关^[1,2]。脂联素(adiponectin, APN)是脂肪细胞特异性分泌的一种蛋白质,新近研究发现脂联素在DR中可能起调控作用。我们将探讨DR患者血清hs-CRP和脂联素水平及关系,了解脂联素在DR中的作用机制,可能对DR患者提供一种新的临床检测指标和治疗手段。

1 对象和方法

1.1 对象 糖尿病组为我院2008-07/2010-02门诊及住院的女性2型糖尿病患者,共136例,纳入标准:(1)体质指数 ≤ 24 ;(2)近期末服用过糖皮质激素及 β -肾上腺素激动剂等药物;(3)无心脑血管并发症。糖尿病的诊断符合1999年世界卫生组织糖尿病的标准。DR诊断依据中华医学会眼科学分会眼底病学组指定的标准,根据眼底镜检查及荧光素眼底血管造影将患者分为3组:(1)非视网膜病变组(No-DR, NDR)49例,年龄 56.2 ± 6.6 岁,病程6mo~10a。(2)非增生性糖尿病视网膜病变组(no-proliferative diabetic retinopathy, NPDR)46例,年龄 61.1 ± 5.2 岁,病程3~15a。(3)增生性糖尿病视网膜病变组(proliferative diabetic retinopathy, PDR)41例,年龄 66.2 ± 6.9 岁,病程5~26a。选择健康女性为正常对照组,共45例,年龄 56.6 ± 7.6 岁,无糖尿病、高血压及其他慢性病史。空腹血糖及口服葡萄糖耐量试验均正常,双眼散瞳检查眼底正常。

1.2 方法 测定身高、体质量,计算体质量指数。受检者禁食8~10h后,晨起抽取空腹静脉血6mL,分成3份,1份血直接送检测空腹血糖(FPG)、胰岛素浓度(INS),其余血离心后,取血清置于-20℃冰箱保存,待测血清脂联素及hs-CRP浓度。空腹血糖(FPG)检测采用葡萄糖氧化酶法,胰岛素测定采用放免法测定。脂联素浓度测定:采用美国Linco公司生产的脂联素(adiponectin, APN)酶免疫吸附法(ELISA)测定试剂盒及日本HT-IR酶标仪,严格按照试剂盒说明书的要求步骤进行操作。血清hs-CRP浓

表1 NDR组、NPDR组、PDR组及对照组血清脂联素、hs-CRP浓度 ($\bar{x} \pm s, \text{mg/L}$)

| 分组 | n | 脂联素 | hs-CRP |
|-------|----|------------------|-----------------|
| 对照组 | 45 | 13.55 ± 5.87 | 2.01 ± 0.85 |
| NDR组 | 49 | 8.76 ± 3.61 | 3.12 ± 1.24 |
| NPDR组 | 46 | 6.22 ± 2.53 | 4.89 ± 1.66 |
| PDR组 | 41 | 3.98 ± 1.86 | 6.95 ± 2.59 |

度检测:采用速率散射比浊法测定,试剂由美国利德曼生化技术有限公司提供。

统计学分析:计量数据采用 $\bar{x} \pm s$ 表示,使用SPSS 11.0统计软件包进行数据分析,多组均数比较采用单因素设计的定量资料的方差分析,多个均数之间两两比较采用 q 检验;相关分析采用直线相关分析。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 NDR组、NPDR组、PDR组患者及对照组受检者血清脂联素、hs-CRP浓度比较 正常对照组与NDR组患者的血清脂联素比较($q = 5.4401, P = 0.000$)、NDR组与NPDR组比较($q = 3.1535, P = 0.002$)、NPDR组与PDR组($q = 4.8756, P = 0.000$)比较,两组之间的差异具有统计学意义(表1)。正常对照组与NDR组患者的血清hs-CRP浓度比较($q = 2.4367, P = 0.0017$)、NDR组与NPDR组比较($q = 2.0572, P = 0.003$)、NPDR组与PDR组($q = 2.6184, P = 0.001$)比较,两组之间的差异具有统计学意义(表1)。

2.2 患者血清hs-CRP与血清脂联素水平之间的相关关系 直线相关分析结果显示:DR患者血清hs-CRP水平与血清脂联素水平呈负相关($r = -0.643, P < 0.01$,表1)。

3 讨论

脂联素亦称Acrp30, AdipoQ或GBP28,是脂肪细胞分泌的一种血浆激素蛋白,在脂肪组织中高度表达并进入血液循环,在血浆中有相对较高的浓度,具有重要代谢功能。循环中的脂联素浓度受到多种因素的影响,如肥胖、昼夜的节律、性别、药物等^[3-5]。我们在排除了以上影响因素以后,发现糖尿病患者血清中脂联素水平明显低于健康对照组,并随着DR病情的加重脂联素水平明显降低,这个结论与以往研究^[6]相似。表明血清脂联素浓度水平在2型糖尿病视网膜病变的发生发展过程中起着重要的作用。

hs-CRP是一种主要由肝脏合成的蛋白质,是人体最敏感的非特异性炎症反应标志物之一,研究表明hs-CRP与糖尿病微血管病变有关^[1,2]。我们发现,DR组患者血清hs-CRP浓度明显高于正常对照组和无DR组,而且PDR组患者血清hs-CRP浓度水平高于NPDR组患者,表明DR患者血清hs-CRP浓度水平的升高与糖尿病视网膜病变的严重程度相关,血清hs-CRP浓度水平愈高,其病变程度愈重。表明炎症反应参与和影响了糖尿病视网膜病变的发生、发展。而DR组患者血清hs-CRP浓度增高与血液中白细胞介素6、肿瘤坏死因子 α 等促炎性反应细胞因子的浓度增高有关^[7]。我们还发现DR患者血清脂联素浓度水平与血清hs-CRP浓度水平存在显著负相关,血清脂联素浓度水平下降,伴随着血清hs-CRP浓度水平的

升高,且与糖尿病视网膜病变的严重程度相关。可以推测:随着血清脂联素浓度水平的下降,导致视网膜血管内皮的炎症反应加重,降低血管细胞间黏附能力,提高血管内皮细胞的增生迁移能力,促进DR的发生。而脂联素抗炎作用的机制在于:(1)脂联素可通过激活cAMP-PKA通路抑制TNF- α 诱导NF- κ B活性,抑制NF- κ B刺激的炎症细胞黏附分子VCAM-1,ICAM-1等表达,降低血管细胞间黏附及迁移^[8]。(2)脂联素也可通过PI3K/Akt途径实现抑制NF- κ B活性,调控炎症因子的表达,发挥对血管内皮的抗炎作用^[9]。(3)脂联素可抑制炎症因子IL-6合成,诱导抗炎因子IL-1,IL-10等产生,抑制血管炎症反应^[10]。

综上所述,我们初步探讨的结果表明,血清APN水平在T2DM患者中明显降低,且合并视网膜血管损伤的T2DM患者下降更明显;血清APN与血清hs-CRP浓度水平存在显著负相关,提示APN是联系炎症反应的纽带;也提示APN是T2DM和糖尿病视网膜病变的保护性因子,其作用的发挥是通过拮抗炎症因子实现的。因此血清脂联素水平的降低或者血清hs-CRP水平的升高为筛查糖尿病危险人群、及早诊治这一病症提供了有力的依据。此外,长期抗炎药物的治疗,将成为改善IR、治疗T2DM的新趋向。

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