

doi: 10.13241/j.cnki.pmb.2018.06.019

血清 Fractalkine、Apelin 水平与糖尿病视网膜病变患者血糖、血脂以及病程的关系研究

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摘要 目的:研究血清 Fractalkine(FKN)、爱帕琳肽(Apelin)水平与糖尿病视网膜病变(DR)患者血糖、血脂以及病程的关系。**方法:**选取我院于2015年1月至2016年12月收治的160例糖尿病患者为研究对象,行眼底荧光造影、裂隙灯显微镜检查,按照检查结果将其区分为非增生型DR组(稳定组,43例)、背景期DR组(背景组,62例)和增殖期DR组(增殖组,55例),另外于同期选取我院40例健康体检者为健康对照组(健康组),测量4组血清FKN、Apelin、空腹血糖(FPG)、餐后2h血糖(2hPG)、糖化血红蛋白(HbA1c)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、甘油三酯(TG)和总胆固醇(TC)水平,使用Pearson相关性分析分析血清FKN、Apelin与FPG、2hPG、HbA1c、HDL-C、LDL-C、TG、TC、糖尿病病程的相关性。**结果:**血清FKN、Apelin水平比较:增殖组>背景组>稳定组>健康组,各组间比较差异具有统计学意义($P<0.05$);血清FPG、2hPG、HbA1c、LDL-C、TG、TC水平比较:增殖组>背景组>稳定组>健康组,各组间比较差异具有统计学意义($P<0.05$);血清HDL-C水平比较:健康组>稳定组>背景组>增殖组,各组间比较差异具有统计学意义($P<0.05$);采用Pearson相关性分析显示,血清FKN水平与FPG、2hPG、HbA1c、LDL-C、TG、TC、糖尿病病程呈正相关性($r=0.321, 0.215, 0.645, 0.154, 0.215, 0.325, 0.578, P<0.05$),与HDL-C呈负相关性($r=-0.547, P<0.05$);血清Apelin水平与FPG、2hPG、HbA1c、LDL-C、TG、TC、糖尿病病程呈正相关性($r=0.245, 0.574, 0.951, 0.357, 0.357, 0.159, 0.546, P<0.05$),与HDL-C呈负相关性($r=-0.459, P<0.05$);糖尿病病程、HbA1c、LDL-C、HDL-C、FKN和Apelin为DR病程的相关影响因素。**结论:**糖尿病伴发DR患者血清FKN、Apelin水平随着病程的加重逐渐增加,且这两种因子的水平与患者血糖、血脂代谢关系密切。

关键词:糖尿病;视网膜病变;Fractalkine;Apelin;血糖;血脂;病程

中图分类号:R587.2 文献标识码:A 文章编号:1673-6273(2018)06-1093-05

Relationship Between Serum Fractalkine and Apelin Levels, Blood Glucose, Blood Lipids and the Course of Disease in Patients with Diabetic Retinopathy

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ABSTRACT Objective: To study the relationship between serum Fractalkine (FKN) and Aipalin peptide (Apelin) levels, blood glucose, blood lipids and the course of disease in patients with diabetic retinopathy (DR). **Methods:** 160 patients with diabetes in our hospital from January 2015 to December 2016 were selected as the research object, fundus fluorescein angiography and slit lamp microscopy were performed, and they were divided into non proliferative group DR (stable group, 43 cases), background group DR (background group, 62 cases) and proliferative stage DR group (proliferation group, 55 cases) according to the results of the test, in addition, 40 healthy people in our hospital were selected as healthy control group (healthy group) at the same period. The levels of serum FKN, Apelin, fasting blood glucose (FPG), 2h postprandial blood glucose (2hPG), glycosylated hemoglobin (HbA1c), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), triglyceride (TG) and total cholesterol (TC) of 4 groups were measured, correlation between serum FKN and Apelin with FPG, 2hPG, HbA1c, HDL-C, LDL-C, TG, TC and the course of diabetes was analyzed by Pearson correlation analysis. **Results:** The levels of serum FKN and Apelin were compared: proliferation group>background group> stable group>healthy group, the difference between each group was statistically significant ($P<0.05$). The levels of serum FPG, 2hPG, HbA1c, LDL-C, TG and TC were compared: proliferation group> background group>stable group>healthy group, the difference between each group was statistically significant ($P<0.05$). The levels of serum HDL-C were compared: healthy group> stable group>background group>proliferation group, the difference between each group was statistically significant ($P<0.05$). Pearson correlation analysis showed that the level of serum FKN was positively correlated with level of FPG, 2hPG, HbA1c, LDL-C, TG,

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(收稿日期:2017-06-18 接受日期:2017-07-15)

TC, the course of diabetes ($r=0.321, 0.215, 0.645, 0.154, 0.215, 0.325, 0.578, P<0.05$), and there was a negative correlation with HDL-C ($r=-0.547, P<0.05$). The serum levels of Apelin was positively correlated with FPG, 2hPG, HbA1c, LDL-C, TG, TC, the course of diabetes ($r=0.245, 0.574, 0.951, 0.357, 0.357, 0.159, 0.546, P<0.05$), and there was a negative correlation with HDL-C ($r=-0.459, p<0.05$). The course of diabetes, HbA1c, LDL-C, HDL-C, FKN and Apelin were related factors influencing the course of DR. **Conclusion:** The levels of serum FKN and Apelin are increased gradually with the aggravation of the course of disease in patients with diabetes mellitus accompanied by DR, and the levels of the two factors are closely related to blood glucose and blood lipid metabolism of patients.

Key words: Diabetes; Retinopathy; Fractalkine; Apelin; Blood glucose; Blood lipid; Course of disease

Chinese Library Classification(CLC): R587.2 Document code: A

Article ID: 1673-6273(2018)06-1093-05

前言

糖尿病是一种以高血糖为表现的代谢性疾病,其长期发展会引发糖尿病肾病、糖尿病视网膜病变(Diabetic retinopathy, DR)、心脏自主神经病变、颅内大血管病变等并发症,其中 DR 是引起糖尿病患者视力低下或致盲的主要原因^[1,2]。糖尿病患者伴发 DR 与血管病变有关,但是其具体发病机制尚不明确,随着分子生物学研究的深入,血清因子 Fractalkine(FKN)、爱帕琳肽(Apelin)被发现在糖尿病病情进展过程中具有重要作用^[3,4]。血清 FKN 于 1997 年被发现,其参与了白细胞吞噬及淋巴细胞游走过程,具有趋化和粘附功能,研究显示其与人体血管异常和心血管疾病发展存在一定相关性^[5-7]。血清 Apelin 是新近发现的由脂肪细胞分泌的脂肪细胞因子,参与了细胞的增殖和迁移过程,其可与体内胰岛素相互作用而对糖尿病的微血管病变起促进作用^[8-10]。本研究通过检测糖尿病患者 FKN 和 Apelin 水平,旨在探讨两种血清因子在糖尿病伴发 DR 患者血糖、血脂及病情进展中的作用。现报道如下:

1 资料与方法

1.1 一般资料

选取 2015 年 1 月至 2016 年 12 月于我院进行就诊的 160 例糖尿病患者为研究对象,行眼底荧光造影、裂隙灯显微镜检查,纳入标准:不合并急性并发症(酮症酸中毒)、无免疫系统疾病(系统性红斑狼疮)、无血液系统疾病;清楚了解该调研方法及过程并同意,且签署知情同意书。排除标准:合并如心脏病、高血压等器质性病变;近期出现全身性炎症。

按照检查结果将其区分为稳定组、背景组和增殖组,其中稳定组 43 例,男 21 例,女 22 例,年龄 56-81 岁,平均年龄(61.25 ± 5.35 岁),体质指数(Body Mass Index, BMI)为 $18-26 \text{ kg/m}^2$,平均 BMI 为(21.91 ± 2.32) kg/m^2 ;背景组 62 例,男 39 例,女 23 例,年龄 54-78 岁,平均年龄(63.25 ± 5.41)岁, BMI 为 $19-27 \text{ kg/m}^2$,平均 BMI 为(22.11 ± 1.22) kg/m^2 ;增殖组 55 例,男 31 例,女 24 例,年龄 45-83 岁,平均年龄(63.25 ± 6.48)岁, BMI 为 $20-28 \text{ kg/m}^2$,平均 BMI 为(21.64 ± 2.12) kg/m^2 。并于同期随机选取我院 40 例健康体检者为健康对照组(健康组),男 20 例,女 20 例,年龄 53-81 岁,平均年龄(62.25 ± 5.54)岁,平均 BMI 为(22.1 ± 2.4) kg/m^2 ,四组年龄、性别构成比、BMI 比较,差异无统计学意义($P>0.05$)。

1.2 方法

所有研究对象禁食 8 h,抽取 4 组研究对象晨起空腹静脉

血,采样量 5 mL,血样于离心机上进行离心 10 min,离心机转速为 3000 r/min,取上层清液,在 -30°C 条件下保存待检,而后采取以下方式进行检测:(1)使用酶联免疫吸附实验(ELISA)对 4 组患者血清 FKN 和 Apelin 水平进行测定,使用试剂盒采购于武昊经贸有限公司;(2)使用全自动生化分析仪(深圳迈瑞医疗器械有限公司)对 4 组患者空腹血糖(FPG)、餐后 2h 血糖(2hPG)、糖化血红蛋白(HbA1c)、高密度脂蛋白胆固醇(HDL-C)、低密度脂蛋白胆固醇(LDL-C)、甘油三酯(TG)和总胆固醇(TC)水平进行测量。

1.3 观察指标

对比 4 组研究对象血清 FKN、Apelin 水平以及 FPG、2hPG、HbA1c、HDL-C、LDL-C、TG、TC 水平,并分析 FKN、Apelin 水平与血糖、血脂各因子以及糖尿病程的关系,筛选 DR 病程的影响因素。

1.4 统计学方法

采用 SPSS22.0 对数据进行处理分析,计量资料以均数 $\pm$ 标准差($\bar{x} \pm s$)形式进行描述,各组间比较使用 t 检验,使用 Pearson 相关性分析患者 FKN、Apelin 水平和其他因素间的关系,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 各组血清 FKN、Apelin 水平比较

4 组血清 FKN、Apelin 水平比较差异有统计学意义($P<0.05$);稳定组、背景组、增殖组血清 FKN、Apelin 水平均高于健康组,并且按照稳定组、背景组、增殖组的顺序递增,组间两两比较差异有统计学意义($P<0.05$)。具体数据分析如表 1。

2.2 各组血糖、血脂水平比较

4 组血清 FPG、2hPG、HbA1c、LDL-C、HDL-C、TC、TG 水平比较差异有统计学意义($P<0.05$);稳定组、背景组、增殖组 FPG、2hPG、HbA1c、LDL-C、TC、TG 水平均高于健康组,并且按照稳定组、背景组、增殖组的顺序递增,组间两两比较差异有统计学意义($P<0.05$);稳定组、背景组、增殖组 HDL-C 水平低于健康组,并且按照稳定组、背景组、增殖组的顺序递减,组间两两比较差异有统计学意义($P<0.05$)。具体数据分析如表 2。

2.3 血清 FKN、Apelin 与其他因素相关性分析

经 Pearson 相关性分析,血清 FKN 水平与 FPG、2hPG、HbA1c、LDL-C、TG、TC、糖尿病病程呈正相关性($r=0.321, 0.215, 0.645, 0.154, 0.215, 0.325, 0.578, P<0.05$),与 HDL-C 呈负相关性($r=-0.547, P<0.05$);血清 Apelin 水平与 FPG、2hPG、HbA1c、LDL-C、TG、TC、糖尿病病程呈正相关性($r=0.245,$

0.574、0.951、0.357、0.357、0.159、0.546, $P<0.05$), 与 HDL-C 呈负相关性($r=-0.459$, $P<0.05$)。

2.4 DR 病程多因素回归分析

多因素回归分析结果显示, 糖尿病病程、HbA1c、LDL-C、HDL-C、FKN 和 Apelin 为 DR 病程的相关影响因素($P<0.05$), 具体如表 3。

表 1 各组血清 FKN、Apelin 水平比较($\bar{x}\pm s$)

Table 1 Comparison of serum FKN and Apelin levels between each groups ($\bar{x}\pm s$)

Groups	n	FKN(ng/mL)	Apelin(ng/mL)
Healthy group	40	0.58± 0.04	3.52± 0.45
Stability group	43	0.67± 0.06 ^a	4.25± 0.65 ^a
Background group	62	0.81± 0.12 ^{ab}	7.35± 1.57 ^{ab}
Proliferation group	55	0.93± 0.21 ^{abc}	9.45± 1.05 ^{abc}
F	-	12.581	15.263
P	-	0.000	0.000

Note: compared with healthy group, ^a $P<0.05$; compared with the stable group, ^b $P<0.05$; compared with background group, ^c $P<0.05$.

表 2 各组间生化指标结果比较($\bar{x}\pm s$)

Table 2 Comparison of biochemical indexes between each groups ($\bar{x}\pm s$)

Groups	n	FPG(mmol/L)	2hPG(mmol/L)	HbA1c(%)	LDL-C(mmol/L)	HDL-C(mmol/L)	TG(mmol/L)	TC(mmol/L)
Healthy group	40	4.64± 0.24	6.39± 0.36	4.25± 0.21	2.53± 0.24	1.71± 0.26	1.64± 0.24	4.36± 0.45
Stability group	43	7.25± 2.25 ^a	10.58± 1.56 ^a	6.97± 0.07 ^a	3.22± 0.59 ^a	1.64± 0.15 ^a	1.71± 0.35 ^a	5.41± 0.68 ^a
Background group	62	8.67± 3.47 ^{ab}	11.68± 3.14 ^{ab}	8.94± 2.54 ^{ab}	3.68± 0.68 ^{ab}	1.34± 0.36 ^{ab}	2.45± 0.25 ^{ab}	5.69± 0.87 ^{ab}
Proliferation group	55	9.58± 4.15 ^{abc}	15.41± 3.46 ^{abc}	10.59± 2.41 ^{abc}	4.64± 0.94 ^{abc}	1.21± 0.14 ^{abc}	2.67± 0.36 ^{abc}	5.94± 0.94 ^{abc}
F	-	12.351	15.025	10.954	10.058	12.145	16.258	10.262
P	-	0.020	0.010	0.000	0.000	0.00	0.01	0.00

Note: compared with healthy group, ^a $P<0.05$; compared with the stable group, ^b $P<0.05$; compared with background group, ^c $P<0.05$.

表 3 DR 病程多因素回归分析

Table 3 Multivariate regression analysis of DR disease course

Variable	Wald	P	OR	95%CI
FKN	6.012	0.024	2.145	1.021-8.214
Apelin	5.168	0.014	1.357	1.231-6.547
HbA1c	4.524	0.012	1.865	1.142-6.524
LDL-C	6.984	0.035	1.259	1.035-5.675
HDL-C	6.241	0.019	0.146	0.125-0.687
Course of diabetes	5.687	0.032	2.173	1.267-6.987

3 讨论

现阶段,我国因病致盲主要原因包括白内障和 DR,随着白内障手术水平的不断提升,DR 势必会成为我国因病致盲的主要因素,早期的 DR 筛查及治疗能够有效降低该病的致盲率,对提高患者生活质量、减轻社会负担具有重要意义^[11,12]。传统的 DR 筛查手段包括视力检查、眼底荧光造影、裂隙灯显微镜检查等,因地域差异和医疗资源分布的不均衡,这些方法在各地的使用率也不尽相同。血清因子检查具有简便、快捷、易操作、地域区别小等优点,在糖尿病 DR 病程确定上显现出一定的优势^[13-15]。

FKN 又名分形素趋化因子,该物质的表达可以使吞噬细胞和淋巴细胞活性增加,使细胞间出现粘附作用,因为该物质能够不依赖整合素而发挥粘附作用,故其发挥作用时间较短,常引起炎症反应,导致血管和组织的损伤^[16-18]。本研究数据显示,糖尿病患者患者的 FKN 水平明显高于健康组,且随着病情的加重 FKN 水平有所提升,并与 FPG、2hPG、HbA1c、LDL-C、TC、TG 呈正相关性($P<0.05$),多元素回归分析结果提示, HbA1c、LDL-C 为血清 FKN 的独立影响因素,提示血糖、血脂和 FKN 共同参与了 DR 病程的发生发展。分析其原因为相比于健康人群,糖尿病患者体内 LDL-C 的糖基化过程更为迅速,生成的人源氧化低密度脂蛋白可以介导血清 FKN 的生成^[19-21]。

糖尿病患者的血糖状态使人体内糖基化终末产物的生成增加,而高血脂状态会使红细胞的变形性变低,提高吞噬细胞如白细胞的游走能力,使其活性增加,导致炎症反应引发血管内皮损伤,而炎症反应的出现会使白细胞介素、肿瘤因子等大量分泌,反馈与血管内皮细胞,引起血清 FKN 的生成^[22-24]。

Apelin 为一种在人体多器官细胞都有表达的多肽,其结构与血管紧张素 II(AngII)的 1 型受体存在较高相似性,该物质是由脂肪细胞分泌,主要作用于中枢神经系统和心血管系统的细胞因子^[25,26]。Apelin 通过作用于心血管平滑肌而参与血压的调节,也可以抑制 AngII 的表达,达到减缓由 AngII 介导的粥样硬化过程的效果^[27,28]。有研究显示^[29],Apelin 在视网膜内皮细胞增殖与新血管形成中起到重要作用,提示其可能对 DR 病情发展具有一定影响。本研究结果提示,糖尿病组患者的 Apelin 水平明显高于健康组,且随着病情的加重 Apelin 水平有所提升,并与 FPG、2hPG、HbA1c、LDL-C、TC、TG 呈正相关性($P<0.05$),多元素回归分析结果提示,HbA1c、LDL-C、HDL-C、FKN 和 Apelin 为 DR 病程的相关影响因素,提示血糖、血脂和 Apelin 共同参与了 DR 病程的发生发展。分析其原因为高血糖状态使糖基化产物在视网膜产生累积,阻碍了氧在视网膜基底细胞间的流通,引发缺氧,而视网膜基底细胞的缺氧会使 Apelin 的表达增加。血脂的异常状态会导致血管内皮细胞的损伤,阻碍视网膜微循环,使 DR 病程加速发展。另外,高血脂状态会引起细胞脂质结构的改变,促使微血栓的形成,使视网膜屏障遭到进一步破坏^[30]。

综上所述,血清 FKN、Apelin、血糖、血脂在 DR 病情发展中起到重要作用,高血糖、高血脂状态加快了 DR 的病程发展,FKN、Apelin 与 DR 病情严重程度存在密切相关,可以作为预测 DR 病程发展及预后的独立因子来使用。

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