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糖尿病肾病(DN)患者血清脂肪特异性丝氨酸蛋白酶抑制剂(Vaspin)水平的变化及其与炎症因子的关系研究*

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摘要 目的:分析糖尿病肾病(Diabetic Nephropathy, DN)患者血清脂肪特异性丝氨酸蛋白酶抑制剂(Vaspin)水平的变化及其与炎症因子的关系。**方法:**将我院近期(2016年10月-2019年10月)收治100例DN患者设置为DN组,依据DN临床进展分期分组,39例白蛋白尿正常者设置为A组,40例早期DN微量蛋白尿者设置为B组,21例临床DN大量蛋白尿者设为C组,并选取同期于我院的健康体检健康者50例设置为健康组。检测和比价各组糖脂代谢水平、血清Vaspin、炎症因子水平,并进行相关性分析。**结果:**四组入组者脂代谢各项指标水平相比差异无统计学意义($P>0.05$)。而DN组中A组、B组、C组患者血清糖代谢水平均明显高于健康组($P<0.05$)。DN组各组Vaspin、TNF- α 、IL-6、MCP-1水平均高于健康组($P<0.05$)。C组、B组、A组IL-6、TNF- α 、MCP-1升高,Vaspin降低($P<0.05$)。A组IL-10水平高于健康组($P<0.05$)。其余各组间比较($P>0.05$)。各组Vaspin水平与促炎因子IL-6、TNF- α 、MCP-1水平呈负相关($P<0.05$),与抗炎因子IL-10水平无关($P>0.05$)。**结论:**随着疾病的严重程度增加, DN患者血清vaspin呈上升趋势,且与患者的炎症因子呈负相关。检测vaspin水平的变化有助于临床对该病的防治。

关键词:糖尿病肾病;血清脂肪特异性丝氨酸蛋白酶抑制剂;炎症因子;相关性

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A Study on the Serum Level of Vaspin and its Relationship with the Inflammatory Factors in Patients with Diabetic Nephropathy*

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ABSTRACT Objective: To analyze the changes of serum lipid-specific serine protease inhibitor (Vaspin) levels in patients with diabetic nephropathy (DN) and its relationship with inflammatory factors. **Methods:** 100 patients with DN who were admitted to our hospital recently (October 2016-October 2019) were set as the DN group, grouped according to the clinical progress of DN, 39 cases of normal albuminuria were set as group A and 40 cases of early DN Microproteinuria patients were set as group B, 21 cases of clinical DN massive proteinuria were set as group C, and 50 healthy subjects who were checked in our hospital during the same period were selected as the healthy group. The glucose and lipid metabolism levels, serum Vaspin, and inflammatory factor levels of each group were detected and compared, and correlation analysis was performed. **Results:** There was no significant difference in the levels of lipid metabolism among the four groups ($P>0.05$). The serum glucose metabolism levels of patients in group A, B and C in DN group were significantly higher than those in healthy group ($P<0.05$). The levels of Vaspin, TNF- α , IL-6 and MCP-1 in the DN group were higher than those in the healthy group ($P<0.05$). IL-6, TNF- α , MCP-1 increased in group C, B and A, and Vaspin decreased ($P<0.05$). The level of IL-10 in group A was higher than that in healthy group ($P<0.05$). Comparison among other groups ($P>0.05$). Vaspin levels in each group were negatively correlated with the levels of pro-inflammatory factors IL-6, TNF- α , and MCP-1 ($P<0.05$), and were not related to the levels of anti-inflammatory factor IL-10 ($P>0.05$). **Conclusion:** As the severity of the disease increases, the serum vaspin of patients with DN is on the rise, and it is negatively correlated with the patient's inflammatory factors. Detection of changes in vaspin levels can help prevent and treat the disease clinically.

Key words: Diabetic nephropathy; Serum fat specific serine protease inhibitor; Inflammatory factors; Relationship study

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前言

随着人们生活方式及饮食结构的改变,2型糖尿病的发病率呈逐年上升的趋势。糖尿病肾病(Diabetic Nephropathy, DN)是糖尿病严重的微血管并发症之一,是引发大多数末期肾病发病的主要危险因素,是糖尿病致死的主要因素。DN的发病机制复杂尚无统一论^[1-3],其最重要的一点是因机体长期处于高血糖水平状态,易发生多系统功能障碍^[4]。研究表明^[5-7]炎症因子与DN的发生发展密切相关。Vaspin是参与糖脂代谢的脂肪因子,同时可调节免疫及炎症反应^[8-10],但Vaspin与DN患者及炎症因子相关性目前尚不明确。基于此,本研究选取我院收治DN患者,依据其临床分期分组,分析了DN患者血清Vaspin水平的变化及其与炎症因子的关系。

1 资料与方法

1.1 一般资料

将我院近期(2016年10月-2019年10月)收治的100例DN患者设置为DN组,依据DN临床进展分期分组,39例白蛋白尿正常者(UAER<30mg/24h)设置为A组,40例早期DN微量蛋白尿者(UAER30~300mg/24h)设置为B组,21例临床DN大量蛋白尿者(UAER持续>300mg/24h)设为C组,并选取同期于我院的健康体检健康者50例设置为健康组。纳入标准:符合2型糖尿病诊断标准;血压水平正常且稳定;血脂控制水平控制良好。排除标准:可能引起尿蛋白排泄率(UAER)升高的疾病;急慢性肾小球肾炎、肾盂肾炎;肾毒性药物;各种感染;尿路梗阻等。其中,A组:男21例(53.85%),女18例(46.15%),病程0.5-14.1年,平均(4.7±0.5)年,年龄31-79岁,平均(59.6±4.2)岁,平均BMI(22.75±2.31)Kg/m²,平均空腹血糖(7.0±0.3)mmol/L,平均血红蛋白(93.5±2.1)g/L,合并症(13±0.2)种。B组:男22例(55.00%),女18例(45.00%),病程0.7-13.6年,平均(5.1±0.4)年,年龄30-79岁,平均(60.1±4.5)岁,平均BMI(22.95±2.42)Kg/m²,平均空腹血糖(7.1±0.2)mmol/L,平均

血红蛋白(92.8±2.2)g/L,合并症(1.4±0.3)种。C组:男12例(57.14%),女9例(42.86%),病程0.3-15.1年,平均(5.3±0.5)年,年龄37-80岁,平均(61.1±3.8)岁,平均BMI(22.96±2.75)Kg/m²,平均空腹血糖(7.3±0.2)mmol/L,平均血红蛋白(92.5±1.2)g/L,合并症(1.5±0.2)种。健康组:男28例(56.00%),女93例(44.00%),年龄39-74岁,平均(59.3±4.1)岁,平均BMI(22.26±2.64)Kg/m²,平均空腹血糖(5.1±0.7)mmol/L,平均血红蛋白(96.5±4.5)g/L。DN组患者一般资料与对照组比较差异均无统计学意义($P>0.05$),具有可比性。

1.2 检测方法

抽取入组者空腹10h以上的晨时静脉血10mL,放置30min于37℃的环境内,离心分离血清。检测糖代谢水平、脂代谢水平,另分离血清后-70℃冷藏,以ELISA法检测Vaspin及炎症因子。其中Vaspin试剂由上海生物科技公司提供,TNF- α 、IL-6、MCP-1和IL-10试剂由北京生物科技有限公司提供,用深圳市盛信康科技有限公司生产,型号SK01酶标分析仪。

1.3 评价标准

对照血清糖脂代谢水平、Vaspin、炎症因子(TNF- α 、IL-6)、IL-10和MCP-1水平,进行相关分析^[11]。

1.4 统计学方法

数据采用SPSS 17.0软件进行,计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用t检验;计数资料以%表示,组间比较采用 χ^2 校验,相关性分析采用Pearson检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 四组血清糖脂代谢指标水平的比较

四组TC、TG、HDL-C、LDL-C脂代谢各项指标水平相比差异无统计学意义($P>0.05$)。而DN组中A组、B组、C组患者FPG、HbA1c血清糖代谢水平均明显高于健康组,差异具有统计学意义($P<0.05$)。详见表1。

表1 四组入组者血清糖脂代谢指标水平比较($\bar{x}\pm s$)

Table 1 Comparison of serum glucose and lipid metabolism indexes among four groups ($\bar{x}\pm s$)

Groups	Number of cases	FPG(mmol/L)	HbA1c(%)	TC(mmol/L)	TG(mmol/L)	HDL-C(mmol/L)	LDL-C(mmol/L)
Group A	39	7.11±0.67*	6.03±0.97*	5.10±0.61	1.35±0.40	1.03±0.26	2.47±0.67
Group B	40	6.89±0.72*	6.06±0.98*	5.17±0.71	1.32±0.38	1.08±0.23	2.41±0.68
Group C	21	7.05±0.76*	6.33±0.95*	5.20±0.67	1.42±0.37	1.01±0.20	2.53±0.71
Health Group	50	5.19±0.59	4.59±0.69	5.06±0.59	1.29±0.33	1.09±0.19	2.30±0.44

Note: Compared with healthy people in the control group, $P^* < 0.05$.

2.2 四组入组者血清Vaspin、炎症因子、抗炎因子水平比较

DN组组内各组Vaspin、TNF- α 、IL-6、MCP-1水平均高于健康组($P<0.05$)。C组、B组、A组IL-6、TNF- α 、MCP-1水平依次升高,Vaspin水平依次降低,各组间比较($P<0.05$)。A组IL-10水平高于健康组($P<0.05$),其余各组间比较($P>0.05$)。详见表2。

2.3 血清Vaspin水平与各炎症因子的相关性

血清Vaspin水平与促炎因子IL-6、TNF- α 、MCP-1呈负相

关($P<0.05$),与抗炎因子IL-1水平无关($P>0.05$)。详见表3。

3 讨论

DN是世界范围内最常见的肾病,其流行程度与全球糖尿病流行率的急剧上升有相似之处,为糖尿病的主要慢性微血管并发症,也是最严重并发症之一^[12]。随着病情进展约有30%左右的患者出现DN临床表现(包括肾小球和管状上皮细胞肥大及微蛋白尿的形成,从而导致肾小球基底膜增厚,血管基质增

表 2 四组血清 Vaspin、炎症因子、抗炎因子水平的比较 ($\bar{x}\pm s$)

Table 2 Comparison of the serum vaspin, inflammatory factor and anti-inflammatory factor among four groups ($\bar{x}\pm s$)

Groups	Number of cases	Vaspin(ng/mL)	TNF- α (pg/mL)	IL-6(pg/mL)	MCP-1(pg/mL)	IL-10(pg/mL)
Group A	39	1.23 \pm 0.39 ^{*#k}	1.97 \pm 0.43 ^{*#k}	2.33 \pm 0.54 ^{#k}	64.92 \pm 8.34 ^{*#k}	3.13 \pm 0.99 [*]
Group B	40	1.79 \pm 0.57 ^{*#}	1.39 \pm 0.33 ^{*#}	1.59 \pm 0.39 ^{*#}	57.84 \pm 7.51 ^{*#}	2.94 \pm 0.91
Group C	21	2.62 \pm 0.63 [*]	0.60 \pm 0.22 [*]	1.37 \pm 0.31 [*]	51.09 \pm 6.42 [*]	2.76 \pm 0.85
Health Group	50	0.79 \pm 0.18	0.44 \pm 0.13	0.79 \pm 0.22	39.28 \pm 5.02	2.06 \pm 0.47

Note: Compared with healthy people in the control group, $P^* < 0.05$; Compared with group C, $P^{\#} < 0.05$; Compared with group B, $P^k < 0.05$.

表 3 Vaspin 与各炎症因子的相关性分析

Table 3 Pearson correlation analysis of vaspin and inflammatory factors

Factor	r	P	OR	95%CI
IL-6	-0.42	0.001	0.638	1.235~15.964
TNF- α	-0.42	0.001	0.638	1.235~15.964
MCP-1	-0.46	0.006	0.531	1.106~13.531
IL-10	0.21	0.087	0.076	0.451~10.276

加和蛋白尿),该病起病较隐匿,被发现时往往已呈现显性白蛋白尿,这其中的 20%患者可进展为终末期肾病,是终末期肾病的常见病因^[13-16]。目前研究认为 DN 发病的主要原因是机体长期处于糖代谢紊乱状态,亦与高血压、遗传、肾小球超滤、环境、较长糖尿病病程、免疫功能降低等多因素有关^[17,18]。有研究显示^[19,24]多种炎症因子均能够直接导致糖脂代谢紊乱,并能够引起胰岛素抵抗,进而加重肾功能损伤。

Vaspin 是 2005 年首次由 Hida 等从 OLETF 大鼠的内脏脂肪组织中分离,属于丝氨酸蛋白酶抑制剂家族成员,也是目前研究较多对胰岛素抵抗发挥抑制作用的脂肪因子。研究显示^[23,24]Vaspin 的水平随着糖尿病并发症的发生而下降。亦有研究报道^[25,26]Vaspin 可能通过影响体内多细胞改变血管内环境。Angelica RN 等^[27]研究选择 T2DM 患者,其中糖尿病白蛋白尿为 DM 组、早期 DN 微量蛋白尿早期 DN 组、临床 DN 大量蛋白尿临床 DN 组,体检健康者为对照组。结果显示与对照组比较,其他各组 Vaspin、TNF- α 、IL-6、MCP-1 水平升高,DM 组、早期 DN 组、临床 DN 组 IL-6、TNF- α 、MCP-1 水平呈依次升高,Vaspin 水平则依次降低。临床 DN 组 IL-10 水平高于对照组 ($P < 0.05$)。Vaspin 与促炎因子 IL-6、TNF- α 、MCP-1 呈负相关 ($P < 0.05$),与抗炎因子 IL-10 无关 ($P > 0.05$)。

本研究显示,糖尿病患者血清 IL-6、TNF- α 、MCP-1 水平比对照组高,并且随着蛋白尿的增加而逐渐升高,说明糖尿病患者本身存在炎症反应,且严重程度与蛋白尿量有关。血清 Vaspin 水平随着蛋白尿水平增加而降低,说明 Vaspin 参与了 DN 的炎症反应进程,IL-10 水平有升高但不显著,另外通过单因素相关分析显示,血清 Vaspin 水平与 TNF- α 、IL-6 和 MCP-1 呈负相关,提示脂肪细胞因子 Vaspin 有一定的抗炎作用,其水平变化与炎症因子密切相关,而本研究尚未针对其具体的作用机制进行有效的研究探讨,本组研究结果与 Qamar, A、Filla、Gilbert 等研究结果相近^[28-30]。

综上所述, DN 患者病情随着疾病的严重程度增加,患者血清 vaspin 呈上升趋势,且血清 Vaspin 水平与患者的炎症因子

呈负水平增加。因此在 DN 患者中,实施对 vaspin 水平、炎症因子的实时监测跟踪,有助于临床对该病的防治提供重要的参考依据。

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(上接第 2320 页)

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