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慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平变化及其临床诊断价值 *

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摘要 目的:分析慢性肾小球肾炎患者血清肝细胞生长因子(HGF)、胱抑素 C(Cys-C)、凝血酶激活的纤溶抑制物(TAFI)水平的变化及其临床诊断价值。**方法:**选择我院 2017 年 1 月~2018 年 5 月收治的 71 例慢性肾小球肾炎患者作为慢性肾小球肾炎组及同期于本院进行健康体检的 83 例作为健康对照组。检测进而比较两组血清 HGF、Cys-C、TAFI 水平,分析以上指标和患者肾功能的相关性及对慢性肾小球肾炎的诊断价值。**结果:**慢性肾小球肾炎组血清 HGF、Cys-C、TAFI 水平均显著高于对照组($P<0.05$)。慢性肾小球肾炎患者治疗后血清 HGF、Cys-C、TAFI 水平均显著低于治疗前($P<0.05$)。慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平和肾功能指标(肌酐(Scr)、尿素氮(BUN)、尿酸(UA))均呈显著正相关(P 均 <0.05)。血清 HGF 水平诊断慢性肾小球肾炎的曲线下面积为 0.826,敏感度和特异度分别为 0.747 和 0.746;血清 Cys-C 水平诊断慢性肾小球肾炎的曲线下面积为 0.821,敏感度和特异度分别为 0.687 和 0.859;血清 TAFI 水平诊断慢性肾小球肾炎的曲线下面积为 0.816,敏感度和特异度分别为 0.855 和 0.647;血清 HGF、Cys-C、TAFI 水平联合检测诊断慢性肾小球肾炎的曲线下面积为 0.951,敏感度和特异度分别为 0.831 和 0.757。**结论:**慢性肾小球肾炎患者血清 HGF、Cys-C 及 TAFI 水平均明显升高,联合检测血清 HGF、Cys-C 及 TAFI 可能作为慢性肾小球肾炎诊断及预评估参考指标。

关键词:慢性肾小球肾炎;肝细胞生长因子;胱抑素 C;凝血酶激活的纤溶抑制物

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Changes of Serum Levels of HGF, Cys-C and Tafi in the Patients with Chronic Glomerulonephritis and Their Clinical Diagnostic Value*

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ABSTRACT Objective: To analyze the changes of serum hepatocyte growth factor (HGF), cystatin C (Cys-C) and thrombin activated fibrinolytic inhibitor (TAFI) in patients with chronic glomerulonephritis and their clinical diagnostic value. **Methods:** 71 cases of chronic glomerulonephritis admitted and treated in our hospital from January 2017 to May 2018 were selected as the chronic glomerulonephritis group and 83 cases of healthy subjects for physical examination in our hospital were selected as the healthy control group. The serum levels of HGF, Cys-C and TAFI in the two groups were compared, the correlation between the above indicators and renal function of patients were analyzed to evaluate their diagnostic value for the chronic glomerulonephritis. **Results:** The serum levels of HGF, Cys-C and TAFI in the chronic glomerulonephritis group were significantly higher than those in the control group ($P<0.05$). The serum levels of HGF, Cys-C and TAFI in patients with chronic glomerulonephritis after treatment were significantly lower than those before treatment ($P<0.05$). The serum levels of HGF, Cys-C, TAFI and renal function indexes (creatinine (Scr), urea nitrogen (BUN), uric acid (UA)) were significantly positively correlated in patients with chronic glomerulonephritis (all $P<0.05$). The area under the curve for the diagnosis of chronic glomerulonephritis by serum HGF level was 0.826, and the sensitivity and specificity were 0.747 and 0.746. The area under the curve for the diagnosis of chronic glomerulonephritis was 0.821, and the sensitivity and specificity were 0.687 and 0.859, respectively. The subcurve area, sensitivity and specificity of serum TAFI in the diagnosis of chronic glomerulonephritis were 0.816, 0.855 and 0.647. The combined detection of serum HGF, cys-c and TAFI levels in the diagnosis of chronic glomerulonephritis was 0.951 under the curve, and the sensitivity and specificity were 0.831 and 0.757. **Conclusion:** The serum levels of HGF, Cys-C and TAFI may be involved in the pathogenesis of chronic glomerulonephritis, which can be used as diagnostic and prognostic indicators for the chronic glomerulonephritis.

Key words: Chronic glomerulonephritis; Hepatocyte growth factor; Cystatin C; Thrombin activated fibrinolytic inhibitor

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前言

慢性肾小球肾炎为原发性的肾小球疾病,其发病隐匿,进展缓慢,以程度不一的水肿、蛋白尿、血尿、高血压、肾功能减退等为主要表现,病情迁延、易反复^[1,2]。已有研究证实^[3,4]慢性肾小球肾炎能够诱导肾组织产生进行性纤维化,损伤肾功能,为终末期肾脏病的独立危险因素之一。明确慢性肾小球肾炎的发生机制,对减轻肾组织损伤程度、逆转疾病转归有着重要价值^[5]。

肝细胞生长因子(HGF)为多效性细胞因子,既往作用主要表现为刺激肝细胞生长,最新研究显示^[6]其在肾脏生理及病理改变中有重要作用。胱抑素 C(Cys-C)是肾小球率过滤的可靠标志物,能够客观反映机体肾功能状态^[6,7]。凝血酶激活的纤溶抑制物(TAFI)是下调纤溶系统的糖蛋白,可调节纤维蛋白溶解及凝血系统平衡,目前临床关于其在心血管疾病、血液系统疾病中的研究较多,但缺乏其在肾脏疾病中作用的报道^[8]。本研究旨在分析慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平变化及其临床诊断价值,以期为此类疾病的诊断及治疗提供更多的参考依据。

1 资料与方法

1.1 一般资料

选择我院 2017 年 1 月~2018 年 5 月收治的 71 例慢性肾小球肾炎患者,入选标准^[9]:经临床表现、病史及实验室检查等确诊为慢性肾小球肾炎;心、脑等系统无明显病变;无结核、感染等疾病;非哺乳期或者妊娠期。排除标准:糖尿病肾病、高血压肾病、紫癜性肾炎等继发性慢性肾病;接受免疫抑制剂、糖皮质激素等治疗。71 例患者中男 38 例,女 33 例;年龄 27~62 岁,

平均病程(2.18±0.46)年。同期选择本院健康体检者 83 例作为健康对照组,男 37 例,女 46 例;年龄 25~61 岁。两组性别、年龄等资料比较无统计学差异($P>0.05$)。

1.2 治疗方法

慢性肾小球肾炎患者均接受积极控制高血压、减少尿蛋白、限制食物中蛋白及磷摄入、细胞毒药物等治疗。采集对照组、慢性肾小球肾炎患者治疗前及治疗结束时空腹外周静脉血 4 mL,用血液分离机按 3000 转/分钟分离 15 分钟,将上清液保存在 -80℃低温箱中待检。采用贝克曼 AU5821 生化分析仪检测患者治疗前甘油三酯(TG)、胆固醇(TC)、白蛋白(ALB)、空腹血糖(FPG)、肌酐(Scr)、尿素氮(BUN)、尿酸(UA)水平。采用酶联免疫法测定患者治疗前后血清 HGF、TAFI 水平。采用增强免疫透射比浊法测定治疗前后患者 CysC 水平。

1.3 统计学分析

数据处理选用 SPSS18.0 软件包,计量资料用($\bar{x} \pm s$)表示,组间比较选用独立样本 t 检验,计数资料用[(例)%]表示,组间比较用 χ^2 检验比较,相关性分析采用 Spearman 相关分析,绘制受试者工作特征曲线(ROC 曲线)分析血清指标对慢性肾小球肾炎的诊断价值,以 $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 两组一般资料比较

两组性别、年龄、呼吸、心率、DBP、SBP、TG、TC、ALB、FPG 比较均无统计学差异($P>0.05$);慢性肾小球肾炎组 DBP、SBP、Scr、BUN、UA 水平显著高于对照组,比较差异有统计学意义($P<0.05$),见表 1。

表 1 两组一般资料的比较($\bar{x} \pm s$, 例(%))

Table 1 Comparison of the general data between the two groups($\bar{x} \pm s$, n(%))

Groups	n	Gender		Age (years)	Respiratory rate (x/min)	Heart rate (x/min)	DBP(mmHg)	SBP(mmHg)	TG(mmHg)
		Male	Female						
Control group	83	37(44.58)	46(55.42)	36.47±4.30	18.96±2.65	82.30±10.52	79.51±9.50	114.20±13.27	2.18±0.26
Chronic glomerulonephritis group	71	38(53.52)	33(46.48)	34.98±5.34	19.63±2.01	80.04±12.09	87.04±12.18 [#]	126.48±16.40 [#]	2.13±0.30

续表($\bar{x} \pm s$)

Continue table($\bar{x} \pm s$)

Groups	n	TC(mmHg)	ALB(g/L)	FPG(mmol/L)	Scr(μmol/L)	BUN(mmol/L)	UA(μmol/L)
Control group	83	3.40±0.53	45.39±5.75	4.98±0.66	58.01±7.94	4.84±0.52	334.10±40.21
Chronic glomerulonephritis group	71	3.55±0.41	43.60±6.77	5.15±0.53	74.29±9.88 [#]	7.90±0.93 [#]	350.92±46.78 [#]

Note: Comparison with control group, [#] $P<0.05$.

2.2 两组组血清 HGF、Cys-C、TAFI 水平比较

慢性肾小球肾炎组血清 HGF、Cys-C、TAFI 水平均显著高于对照组,差异有统计学意义($P<0.05$),见表 2。

2.3 慢性肾小球肾炎患者治疗前后血清 HGF、Cys-C、TAFI 水平比较

慢性肾小球肾炎患者治疗后血清 HGF、Cys-C、TAFI 水平

低于治疗前,差异有统计学意义($P<0.05$),见表 3。

2.4 慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平和肾功能指标相关性分析

慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平和肾功能指标(Scr、BUN、UA)均呈显著正相关,见表 4。

表 2 两组血清 HGF、Cys-C、TAFI 水平的比较($\bar{x} \pm s$)Table 2 Comparison of the serum levels of HGF, Cys-C and TAFI between the two groups($\bar{x} \pm s$)

Groups	n	HGF(pg/mL)	Cys-C(mg/L)	TAFI(mg/L)
Control group	83	187.24 $\pm$ 28.91	0.62 $\pm$ 0.13	6.54 $\pm$ 0.89
Chronic glomerulonephritis group	71	410.33 $\pm$ 56.33 [#]	1.15 $\pm$ 0.19 [#]	12.70 $\pm$ 1.65 [#]

Note: Compared with control group, [#] $P < 0.05$.

表 3 慢性肾小球肾炎患者治疗前后血清 HGF、Cys-C、TAFI 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum levels of HGF, Cys-C and TAFI in patients with chronic glomerulonephritis before and after treatment($\bar{x} \pm s$)

Time	n	HGF(pg/mL)	Cys-C(mg/L)	TAFI(mg/L)
Before treatment	71	410.33 $\pm$ 56.33	1.15 $\pm$ 0.19	12.70 $\pm$ 1.65
After treatment	71	268.41 $\pm$ 25.11 ^a	0.78 $\pm$ 0.09 ^a	7.59 $\pm$ 0.94 ^a

Note: Compared with before treatment, ^a $P < 0.05$.

表 4 慢性肾小球肾炎患者血清 HGF、Cys-C、TAFI 水平和肾功能指标的相关性

Table 4 Correlation of serum levels of HGF, Cys-C, TAFI with the renal function indicators of patients with chronic glomerulonephritis

Indicators	Scr(μ mol/L)		BUN(mmol/L)		UA(mol/L)	
	r	P	r	P	r	P
HGF	0.419	0.009	0.380	0.019	0.375	0.026
Cys-C	0.411	0.014	0.402	0.016	0.360	0.031
TAFI	0.430	0.002	0.369	0.027	0.423	0.015

2.5 血清 HGF、Cys-C、TAFI 水平诊断慢性肾小球肾炎的 ROC 曲线分析

血清 HGF 水平诊断慢性肾小球肾炎的曲线下面积为 0.826,敏感度和特异度分别为 0.747 和 0.746;Cys-C 水平诊断慢性肾小球肾炎的曲线下面积为 0.821,敏感度和特异度分别

为 0.687 和 0.859;TAFI 水平诊断慢性肾小球肾炎的曲线下面积为 0.816,敏感度和特异度分别为 0.855 和 0.647;血清 HGF、Cys-C、TAFI 水平联合检测诊断慢性肾小球肾炎的曲线下面积为 0.951,敏感度和特异度分别为 0.831 和 0.757,见表 5 及图 1。

表 5 血清 HGF、Cys-C、TAFI 联合测定慢性肾小球肾炎的 ROC 曲线

Table 5 ROC curve of serum HGF, Cys-C and TAFI combined to determine chronic glomerulonephritis

Indicator	Area	SE	Sig	95%CI		Sensitivity	Specificity	Cutoff
				Lower limit	Upper limit			
HGF	0.826	0.033	0.000	0.762	0.891	0.747	0.746	0.537
Cys-C	0.821	0.035	0.000	0.758	0.894	0.687	0.859	0.663
TAFI	0.816	0.034	0.000	0.749	0.883	0.855	0.647	0.435
Joint	0.951	0.017	0.000	0.918	0.983	0.831	0.957	0.757

3 讨论

慢性肾小球肾炎的发生率高,容易合并多种并发症,个体差异性及疾病复杂性较明显,有关其生理病理的改变为临床研究的难点,目前缺乏统一理论^[10,11]。肾穿刺活检为慢性肾小球肾炎诊断的黄金标准,但其侵入性相对较强,患者难以接受,临床应用受到一定限制^[12,13]。Scr、BUN、UA 及 GFR 等肾功能指标虽可一定程度的反映机体肾功能状态,但特异度及敏感度较低,病情评估价值有限^[14,15]。

HGF 为既往研究发现的可诱导肝细胞生长的因子,随后研究证实其可刺激黑色素瘤、角质细胞及肾小管细胞的 DNA 合成^[19]。最新研究报道^[20]肾组织中 HGF 水平显著高于肝脏组

织,且在肾脏胚胎发生、发育及生理病理中有重要作用。HGF 可显著改善肾小球血流动力学,下调肾小球毛细血管压力,从而抑制毛细血管扩张,改善肾小球高滤过状态,且可特异性的参与血管内皮细胞作用,通过修复及再生肾小球毛细血管利于受损肾小球的恢复^[21]。肾脏正常状态下,内源性 HGF 可通过促有丝分裂作用,保持肾脏正常的功能及结构,减轻肾小球损伤。肾损伤时 HGF 浓度明显上升,通过血液循环进入损伤肾组织,参与肾小管上皮细胞增生,利于组织修复^[22]。本研究结果显示慢性肾小球肾炎组血清 HGF 浓度显著高于健康对照组,经正规、系统的治疗病情好转后血清 HGF 浓度相应降低,说明 HGF 在慢性肾小球肾炎诊治中极为重要,可能和肾损伤修复有关。相关性分析结果显示 HGF 和肾功能指标之间有良好的相关性,

进一步的 ROC 曲线分析发现 HGF 曲线下面积为 0.826, 说明其对慢性肾小球肾炎的准确度较高, 可能是其诊断的灵敏指标。

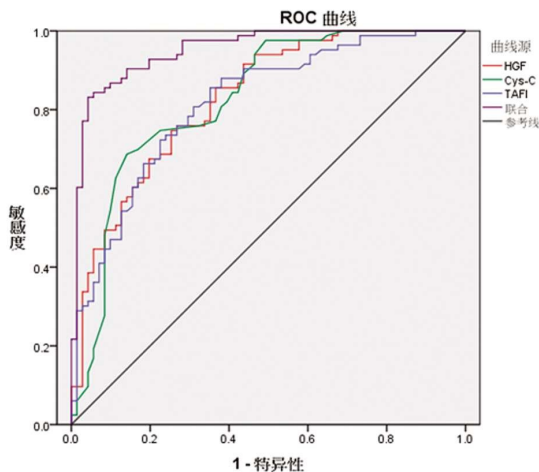


图 1 血清 HGF、Cys-C、TAFI 单独检测和联合检测诊断慢性肾小球肾炎的 ROC 曲线

Fig.1 ROC curve of the detection of serum HGF, Cys-C and TAFI levels in the diagnosis of chronic glomerulonephritis

Cys-C 作为一种分泌性蛋白质, 是半胱氨酸蛋白酶的抑制剂, 其产生比较恒定, 几乎能于任何有核细胞中进行恒定、持续的转录和表达, 且年龄、饮食、营养状态等对其无影响^[23,24]。Cys-C 仅在肾脏中代谢、滤过, 其分子量小, 能够于肾小球滤过膜中自由通过, 几乎可于近曲小管中进行完全重吸收, 进而分解代谢^[25,26]。血清 Cys-C 可于肾小球轻度损害时升高, 能够利于早期肾损害的了解^[27,28]。本研究结果显示慢性肾小球肾炎患者血清 Cys-C 浓度较高, 治疗后其水平显著下降, 说明通过测定患者血清 Cys-C 浓度能够一定程度的反映疾病转归状态。进一步分析发现慢性肾小球肾炎患者血清 Cys-C 水平和肾功能指标均呈正相关, 随着肾功能的恶化血清 Cys-C 浓度相应增加, 说明血清 Cys-C 和此类患者肾功能有良好的一致性。ROC 曲线证实 Cys-C 对慢性肾小球肾炎的诊断价值较高。

国外研究报道^[29,30] 慢性肾小球肾炎能够增加血液高凝状态, 加大血栓形成风险, 从而影响肾小球滤过率, 加重肾功能损伤。TAFI 为纤溶系统的负性调控因子, 可抑制纤溶酶生成, 限制纤溶反应。另有研究发现^[31,32] TAFI 可抑制肾脏纤维蛋白原溶解, 增加肾小球内高凝状态, 诱导局部血小板的黏附, 破坏毛细血管内皮细胞表层完整性, 刺激血小板分泌组织因子, 破坏基底膜电荷屏障或者机械屏障, 增加尿蛋白滤出, 引起肾小球损伤。本结果显示慢性肾小球肾炎组治疗前血清 TAFI 水平较对照组高, 治疗后呈下降趋势, 说明慢性肾小球肾炎患者血液可能存在高凝状态, 通过测定血清 TAFI 水平不仅有利于疾病诊断, 且可反映临床治疗效果。ROC 曲线分析显示 TAFI 曲线下面积为 0.816, 敏感度及特异度分别为 0.855 及 0.647, 说明其在慢性肾小球肾炎诊断中有着较高的诊断效能。同时, 本研究发现联合测定 ROC 曲线下面积明显高于单个测定指标, 说明共同测定其水平能够提高临床诊断率。

综上所述, 慢性肾小球肾炎患者血清 HGF、Cys-C 及 TAFI 水平均明显升高, 联合检测血清 HGF、Cys-C 及 TAFI 可能作为慢性肾小球肾炎诊断及预评估参考指标。但本研究存在样本量

有效、观察指标不够全面等不足, 因此研究结果有待于更多大规模、大样本的研究进一步证实。

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