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血清 RBP4、NGAL、Klotho 蛋白在慢性肾脏病病情监测及预后评估中的价值 *

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摘要 目的：探讨血清视黄醇结合蛋白 4（retinol binding protein 4，RBP4）、中性粒细胞明胶酶相关脂质运载蛋白（neutrophil gelatinase-associated lipocalin，NGAL）、Klotho 蛋白在慢性肾脏病病情监测及预后评估中的价值。**方法：**收集我院 2017 年 5 月 ~2019 年 2 月收治的 297 例慢性肾脏病患者为研究对象，依据肾小球滤过率（GFR）分为 1 期 24 例、2 期 46 例、3 期 128 例、4 期 66 例、5 期 33 例，并依据临床转归情况分为肾功能稳定组 104 例和肾功能恶化组 193 例；同期选择门诊健康体检者 251 例作为对照组。比较各组血清 RBP4、NGAL、Klotho 蛋白表达情况，并分析慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白和 GFR 的相关性。**结果：**慢性肾脏病组血清 RBP4、NGAL 水平高于对照组，Klotho 蛋白低于慢性肾脏病组（P<0.05）。慢性肾脏病 5 期者血清 RBP4、NGAL 水平高于 4 期、3 期、2 期及 1 期者，Klotho 蛋白低于 4 期、3 期、2 期及 1 期者，差异有统计学意义（P<0.05）。慢性肾脏病患者血清 RBP4、NGAL 和 GFR 呈负相关，Klotho 蛋白和 GFR 呈正相关（P<0.05）。肾功能恶化组血清 RBP4、NGAL 水平高于肾功能稳定组，Klotho 蛋白低于肾功能稳定组，差异有统计学意义（P<0.05）。**结论：**血清 RBP4、NGAL 及 Klotho 蛋白表达水平的变化对了解慢性肾脏病患者病情程度及预后评估中有重要的参考价值，建议临床予以重视。

关键词：慢性肾脏病；视黄醇结合蛋白 4；中性粒细胞明胶酶相关脂质运载蛋白；Klotho 蛋白；病情监测；预后

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Serum Levels of RBP4, NGAL, Klotho in Monitoring of Chronic Kidney Disease and Their Roles in Prognosis Evaluation*

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ABSTRACT Objective: To investigate the value of serum levels of retinol binding protein 4 (RBP4), neutrophil gelatinase-associated lipocalin (NGAL) and Klotho protein in monitoring of chronic kidney disease and their roles in prognosis evaluation. **Methods:** 297 patients with chronic kidney disease admitted to our hospital from May 2017 to February 2019 were collected as research objects. According to glomerular filtration rate (GFR), they were divided into 24 cases in phase 1, 46 cases in phase 2, 128 cases in phase 3, 66 cases in phase 4 and 33 cases in phase 5. According to clinical outcome, they were divided into 104 cases in stable renal function group and 193 cases in deteriorated renal function group. 251 healthy outpatients were selected as control group at the same time. The expressions of serum RBP4, NGAL and Klotho proteins in each group were compared, and the correlation between serum RBP4, NGAL, Klotho proteins and GFR in patients with chronic kidney disease was analyzed. **Results:** The levels of serum RBP4 and NGAL in CKD group were higher than those in control group, and the level of Klotho protein was lower than that in CKD group (P<0.05). The levels of serum RBP4 and NGAL in patients with chronic kidney disease stage 5 were higher than those in stages 4, 3, 2 and 1, while Klotho protein was lower than those in stages 4, 3, 2 and 1, the difference was statistically significant (P<0.05). The levels of serum RBP4, NGAL and GFR were negatively correlated, serum Klotho protein and GFR were positively correlated (P<0.05). The levels of serum RBP4 and NGAL in renal function deterioration group were higher than those in renal function stabilization group, and the level of Klotho protein was lower than those in renal function stabilization group, the difference was statistically significant (P<0.05). **Conclusion:** The changes of the levels of serum RBP4, NGAL and Klotho proteins have important reference values in understanding the severity and prognosis of chronic kidney disease patients, which should be paid attention to in clinical experiences.

Key words: Chronic kidney disease; Retinol binding protein 4; Neutrophil gelatinase-associated lipocalin; Klotho protein; Disease surveillance; Prognosis

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前言

慢性肾脏病是因各种因素导致的慢性肾脏结构和功能障碍，尽早发现并干预能够降低此类疾病的并发症、改善患者预后[1]。慢性肾脏病 3 期之前，患者症状较轻微或无任何表现，随着疾病进一步加重，可导致肾功能衰竭，产生中枢神经系统障碍、严重高钾血症、急性心衰等并发症，危及患者生命安全[2,3]。目前临床实践中主要通过蛋白尿水平、肾小球滤过率及血肌酐浓度监测疾病进展程度，但是以上指标无法准确反映疾病早期的病变情况 [4,5]。视黄醇结合蛋白 4（Retinol binding protein 4, RBP4）作为一种脂肪细胞因子，可参与机体血管内皮损害、慢性炎症反应、胰岛素抵抗等反应[6]。有研究认为肾脏为 RBP4 的主要代谢场所，慢性肾脏病患者血清 RBP4 浓度慢性上升，可能为诊断肾功能损伤的特异标志物[7]。又有研究发现[8]，肾功能早期损伤时，中性粒细胞明胶酶相关脂质运载蛋白（Neutrophil gelatinase-associated lipocalin, NGAL）能够结合铁转运蛋白参与铁代谢，调控肾上皮细胞的增生、分化及凋亡，在早期监测、识别慢性肾脏病上有一定优势。Klotho 蛋白主要在肾小管上皮细胞中表达，其对肾脏有一定保护作用，临床研究发现[9]，急性肾功能损伤时 Klotho 蛋白浓度明显下降。本研究探讨血清 RBP4、NGAL、Klotho 蛋白在慢性肾脏病病情监测及预后评估中的价值，结果报告如下。

1 资料与方法

1.1 一般资料

收集我院 2017 年 5 月 ~2019 年 2 月收治的 297 例慢性肾脏病患者作为研究对象，纳入标准：符合慢性肾脏病的诊断标准 [10]：肾脏结构及功能异常超过 3 个月，肾小球滤过率（Glomerular filtration rate, GFR）低于 60 mL/min。排除标准：急性肾功能受损；脑肝肺等脏器明显病变；严重感染；合并自身免疫性疾病；既往接受血液透析、肾脏移植治疗；近 2 个月有输血史；恶性肿瘤；妊娠或哺乳期妇女。297 例慢性肾脏病患者中年龄（22~71）岁，平均（55.19± 6.26）岁；男 162 例，女 135 例；疾病类型：肾小管 - 间质疾病 23 例，继发性肾小球病 57 例，糖尿病肾病 13 例，原发性肾小球病 204 例；疾病分期：1 期（GFR≥ 90 mL/min/1.73 m^2）24 例，2 期（GFR60~89 mL/min/1.73 m^2）46 例，3 期（GFR30~59 mL/min/1.73 m^2）128 例，4 期（GFR15~29 mL/min/1.73 m^2）66 例，5 期（<15 mL/min/1.73 m^2）33 例。同期选择 251 例健康体检合格者为对照组（无近期接受肾毒性药物史，无急慢性肾脏疾病史），年龄（22~73）岁，平均（53.95± 7.42）岁；男 132 人、女 119 人。慢性肾脏病组和对照组年龄、性别比较无统计学差异（P>0.05）。

1.2 试剂和仪器

RBP4 化学发光免疫分析试剂盒购自上海信裕生物科技有限公司，批号：20170104。NGALELISA 检测试剂盒购自武汉伊莱瑞特生物科技股份有限公司，批号：20161012；可溶性 α-Klotho 蛋白 ELISA 检测试剂盒购自研域（上海）化学试剂有限公司，批号：20161218。肾动态显像法检测 GFR 所用实验仪器为德国西门子公司提供的 E.CAM Gantry single head-V2.5 单探头 SPECT，配置低能通用型准直器；药物安全型三通管，北京原子高科股份有限公司提供裂变的[99Tcm]发生器，试剂：注射用亚锡喷替酸（DTPA）由无锡市江原实业技贸总公司提供，批号：20161124。

1.3 检测方法

采集对照组、慢性肾脏病患者随访前及随访结束时空腹静脉血 4 mL，分离血清。用化学发光免疫分析法检测 RBP4 浓度，用酶联免疫吸附法检测 NGAL、Klotho 蛋白浓度。用肾动态显像法检测 GFR 情况。

1.4 随访方法

慢性肾脏病患者均进行 12 个月随访，均进行系统、正规治疗。随访期间 GFR 较基线 GFR 下降超过 30%，或病情进展至需透析治疗的终末期肾病或死亡均判定为肾功能恶化；反之为肾功能稳定[10]。

1.5 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，两组间选用 t 检验，多组间选用方差分析，计数资料用[例（%）]表示，用 x^2 检验比较，相关性分析选用 Pearson 检验，P<0.05 表示差异有统计学意义。

2 结果

2.1 慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白表达水平

慢性肾脏病组血清 RBP4、NGAL 水平高于对照组，Klotho 蛋白低于慢性肾脏病组（P<0.05），见表 1。

表 1 慢性肾脏病组血清 RBP4、NGAL、Klotho 蛋白表达水平检测结果（$\bar{x}\pm s$）

Table 1 Analysis of serum RBP4, NGAL, Klotho proteins in control group and chronic kidney disease group（$\bar{x}\pm s$）

Groups	n	RBP4（μg/L）	NGAL（ng/mL）	Klotho proteins（U/L）
Control group	251	34.17± 4.26	102.19± 6.82	148.96± 18.93
Chronic kidney disease group	297	198.19± 24.45#	319.05± 40.28#	55.04± 7.71#

VS control group, #P<0.05.

2.2 不同分期慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白表达水平

慢性肾脏病 5 期患者血清 RBP4、NGAL 水平高于 4 期、3 期、2 期及 1 期者，Klotho 蛋白低于 4 期、3 期、2 期及 1 期者，差异有统计学意义（P<0.05），见表 2。

2.3 慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白和 GFR 的相关性分析

慢性肾脏病患者血清 RBP4、NGAL 和 GFR 呈负相关，Klotho 蛋白和 GFR 呈正相关（P<0.05），见表 3。

表 2 不同分期慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白分析($\bar{x}\pm s$)

Table 2 Analysis of serum RBP4, NGAL, Klotho proteins in patients with chronic kidney disease of different stages($\bar{x}\pm s$)

Groups	n	RBP4(μg/L)	NGAL(ng/mL)	Klotho proteins(U/L)
Phase 1	24	73.19± 9.77abcd	152.19± 23.91abcd	128.96± 16.82abcd
Phase 2	46	118.35± 13.26abc	200.08± 30.27abc	87.95± 13.29abc
Phase 3	128	167.42± 20.14ab	297.05± 35.21ab	54.04± 7.85ab
Phase 4	66	243.09± 30.69a	395.03± 49.38a	28.05± 3.65a
Phase 5	33	429.94± 54.96	539.61± 67.60	13.26± 0.88
F		896.22	475.91	903.44
P		<0.001	<0.001	<0.001

VS Phase 5, [a]*P*<0.05; VS Phase 4, [b]*P*<0.05; VS Phase 3, [c]*P*<0.05; VS Phase 2, [d]*P*<0.05.

表 3 慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白和 GFR 的相关性分析

Table 3 Analyses the correlation between serum RBP4, NGAL, Klotho protein and GFR in patients with chronic kidney disease

		RBP4	NGAL	Klotho protein
GFR	r	-0.562	-0.603	0.519
	P	0.000	0.000	0.000

2.4 不同预后慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白分析

肾功能恶化组血清 RBP4、NGAL 水平高于肾功能稳定组，Klotho 蛋白低于肾功能稳定组（*P*<0.05），见表 4。

表 4 不同预后慢性肾脏病患者血清 RBP4、NGAL、Klotho 蛋白分析($\bar{x}\pm s$)

Table 4 analysis of serum RBP4, NGAL, Klotho proteins in patients with chronic kidney disease with different prognosis($\bar{x}\pm s$)

Groups	n	RBP4(μg/L)	NGAL(ng/mL)	Klotho proteins(U/L)
Renal function stabilization group	104	83.73± 12.41*	221.21± 31.47*	88.41± 12.81*
Renal function deterioration group	193	259.87± 30.94	371.77± 45.03	37.06± 4.96

VS Renal function deterioration group, **P*<0.05.

3 讨论

慢性肾脏病的发生率及死亡率高，发病隐匿，现已成为公共健康问题的主要类型之一。既往研究表明[11,12]，轻、中度慢性肾脏病患者经及时有效治疗后能够延缓、停止或逆转慢性肾衰竭的进展，防治慢性肾衰竭终末阶段的发生。因此早期诊治对于延缓慢性肾脏病进展有重要作用。外源性肾小球滤过功能测定虽可准确反映肾小球清除率，但价格昂贵、操作较复杂，且具放射性[13]。尿素氮浓度易受到多种因素的影响，机体营养状况、性别及年龄等又可影响血清肌酐浓度，且机体 GFR 正常时，血清肌酐的敏感性较低[14]。内生肌酐清除率（Endogenous creinine clearance rate, CCr）能够直观反映肾小球滤过率情况，但需留取多个时间段的尿液，患者依从率不高。有研究发现[15]，部分血清生物学指标可能在慢性肾脏病监测、治疗及预后中有一定价值。

RBP4 主要由肝细胞合成，在机体尿液、血清中广泛分布，可增加视黄醇的溶解性及稳定性，抑制视黄醇特异性氧化，调节视黄醇在血液中的表达[16]。近年来有研究发现[17,18]，RBP4 也可参与肥胖、肾脏疾病等发生。动物实验模型发现[19]，急性肾衰竭小鼠 RBP 浓度明显增加。健康人群 RBP4 能够在肾脏中被快速清除，但慢性肾脏病患者因滤过低分子量蛋白能力降低，可导致 RBP4 蓄积，增加 RBP4 浓度[20]。Fernando BNTW 等[21]报道 RBP4 浓度和机体 GFR 呈负相关，与血清肌酐浓度呈正相关。以上研究表明，RBP4 浓度和机体肾功能有一定关系。本次研究结果显示，慢性肾脏病患者血清 RBP4 浓度显著高于健康对照组，随着慢性肾脏病分期的不断增加，RBP4 浓度相应上升，提示随着疾病的进展，RBP4 浓度呈递增趋势。GFR 是评价肾功能的主要指标，能够反映肾脏对血液中有害物质的清除能力，GFR 下降程度和患者预后有直接关系。相关性分析发现，RBP4 浓度和 GFR 呈负相关，有较强的相关性。我们随访发现，肾功能稳定组随访前 RBP4 浓度较肾功能恶化组低，且肾功能稳定组随访前后差值相对较小，提示 RBP4 浓度能够间接反映慢性肾脏病患者预后情况。

NGAL 为脂质运载蛋白，可参与机体炎症反应、脂质代谢、免疫应答等反应。NGAL 又属载铁蛋白，和肾脏发育有直接关系，能够参与胚胎肾脏生长发育及基本结构的形成[22]。机体正常状态下 NGAL 浓度较低，肾脏病变时活性游离铁在肾上皮细胞及肾小管液中堆积，刺激 NGAL 表达，是肾脏受损后血液中变化最快的蛋白质[23]。NGAL 经受体介导作用进入机体炎症细胞，与细胞内铁结合，诱导凋亡基因的表达，减轻炎症反应，从而保护肾脏功能[24]。慢性肾小管细胞受损能够促进肾间质中性粒细胞凋亡，导致 NGAL 大量分泌[25]。肾毒性或缺血性所致的急性肾功能损伤早期，NGAL 即可在肾脏大量表达，并释放

至血液及尿液中,且其表达不容易受到药物、肾外因素的影响[26]。本次研究结果发现，慢性肾脏病患者 NGAL 浓度较对照组显著上升，提示 NGAL 浓度能够一定程度的反映慢性肾脏病的发生。慢性肾脏病患者依据不同分期分层后显示,慢性肾脏病 5 期患者 NGAL 浓度显著高于 4 期、3 期、2 期及 1 期者，表明随着疾病的进展,NGAL 水平相应增加，临床通过测定 NGAL 浓度能够利于病情程度的监测。相关性分析发现,NGAL 浓度和机体肾功能相关。进一步分析显示，肾功能稳定组随访前 NGAL 水平,及随访前后 NGAL 差值相对较低,表明通过测定 NGAL 水平对患者预后评价有一定作用。

Klotho 蛋白具有多种生理功能，能够提高机体抗衰老、抗细胞凋亡作用,又可参与机体抑制氧化应激、抑制炎症反应发生、钙磷稳态等反应[27,28]。Klotho 蛋白主要在肾小管上皮细胞中表达,肾脏能够调节 Klotho 蛋白的降解、代谢,是维持 Klotho 蛋白动态平衡的主要脏器[29]。因此推测 Klotho 蛋白的异常表达可能和肾脏疾病紧密相关。 Klotho 蛋白能够抑制 β- 连环蛋白活化,从而改善单侧输尿管梗阻小鼠的肾间质纤维化及肾损伤[30]。慢性肾脏病患者 Klotho 蛋白较健康正常者低,且随着疾病的不断进展,Klotho 蛋白相应减少，可能是肾功能恶化的参考指标[31]。慢性肾脏病患者 Klotho 蛋白表达减少可能与机体的炎性反应有关,一方面 Klotho 蛋白能够缓解炎症反应,另一方面机体炎症细胞因子又可调节 Klotho 蛋白的表达，炎症反应能够降低 Klotho 蛋白表达,影响 Klotho 蛋白转录[32]。本次研究结果显示,Klotho 蛋白在慢性肾脏病患者中的表达显著低于健康对照组，随着疾病分期的增加,Klotho 蛋白相应下降，提示 Klotho 蛋白能够反映慢性肾脏病的严重程度。此外，Klotho 蛋白能够参与甲状旁腺激素的表达,并通过跨膜钙离子转运体调控细胞外钙离子表达,参与机体钙磷代谢的和调节[33,34]。Lee AK 等[35]研究指出,钙磷代谢异常是慢性肾脏病患者心血管受损的主要危险因素，而心血管疾病又是慢性肾脏病的主要并发症，且为此类患者死亡的独立危险因素。推测 Klotho 蛋白异常表达可能与慢性肾脏病患者预后有关。本研究随访结果显示,肾功能恶化组 Klotho 蛋白明显低于肾功能稳定组，证实 Klotho 蛋白和患者预后有关。但本研究随访时间较短,有待进一步研究证实。

综上所述,血清 RBP4、NGAL 及 Klotho 蛋白表达水平的变化对慢性肾脏病患者病情程度及预后评估有重要的参考价值。

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（上接第 3391 页）

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