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·临床研究·

尿神经突起导向因子 1、肾损伤分子 -1、视黄醇结合蛋白水平与妊娠期高血压疾病早期肾损伤的关系研究 *

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摘要 目的：研究尿神经突起导向因子 1（Netrin-1）、肾损伤分子 -1（Kim-1）、视黄醇结合蛋白（RBP）水平与妊娠期高血压疾病（HDCP）早期肾损伤的关系。**方法：**将我院从 2017 年 2 月～2020 年 2 月收治的 HDCP 患者 80 例纳入研究，按照 HDCP 严重程度分作妊娠期高血压组 22 例、轻度子痫前期组 32 例、重度子痫前期组 26 例，另随机选取同期于我院接受规律孕产检以及分娩正常妊娠孕妇 40 例作为正常妊娠组，检测并比较各组尿 Netrin-1、Kim-1、RBP 水平。此外，将 HDCP 患者按照是否出现早期肾损伤分作肾功能损伤组 42 例和肾功能正常组 38 例，比较两组尿 Netrin-1、Kim-1、RBP 以及肾功能指标水平，并进行相关性分析，通过 Logistic 回归分析 HDCP 早期肾损伤的影响因素。**结果：**正常妊娠组、妊娠期高血压组、轻度子痫前期组、重度子痫前期组尿 Netrin-1 水平呈逐渐降低趋势，而尿 Kim-1、RBP 水平均呈逐渐升高趋势，多组数据间两两对比差异均有统计学意义（均 $P<0.05$）。肾功能损伤组尿 Netrin-1 水平低于肾功能正常组，而尿 Kim-1、RBP 以及血尿素氮、血肌酐、24 h 尿白蛋白排出量（UAE）水平均明显高于肾功能正常组（均 $P<0.05$）。经 Pearson 相关性分析可得：HDCP 早期肾损伤患者尿 Netrin-1 水平和血尿素氮、血肌酐、UAE 均呈负相关关系，而 Kim-1、RBP 水平和血尿素氮、血肌酐、UAE 均呈正相关关系（均 $P<0.05$）。经 Logistic 回归分析发现：尿 Netrin-1 是 HDCP 早期肾损伤的保护因素，而尿 Kim-1、RBP 是 HDCP 早期肾损伤的危险因素（均 $P<0.05$）。**结论：**随着尿 Netrin-1 水平的降低以及 Kim-1、RBP 水平的升高，HDCP 早期肾损伤风险越高，检测尿 Netrin-1、Kim-1、RBP 水平可能有助于评估 HDCP 的病情严重程度和肾功能损伤。

关键词：妊娠期高血压疾病；神经突起导向因子 1；肾损伤分子 -1；视黄醇结合蛋白；影响因素

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Study on the Relationship between Urinary Neurite Guidance Factor 1, Kidney Damage Molecule-1, Retinol Binding Protein Levels and Early Renal Damage in Hypertensive Disorder Complicating Pregnancy*

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ABSTRACT Objective: To study the relationship between urinary neurite guidance factor 1 (Netrin-1), kidney injury molecule-1 (KIM-1) and retinol binding protein (RBP) levels and early renal injury in hypertensive disorder complicating pregnancy (HDCP). **Methods:** A total of 80 patients with HDCP who were admitted to our hospital from February 2017 to February 2020 were included in this study. According to the severity of HDCP, the patients were divided into gestational hypertension group with 22 cases, mild preeclampsia group with 32 cases and severe preeclampsia group with 26 cases. Another 40 cases of normal pregnant women who received regular pregnancy and childbirth tests in our hospital during the same period were randomly selected as the normal pregnancy group. The urinary Netrin-1, Kim-1 and RBP levels in each group were detected and compared. In addition, patients with HDCP were divided into renal function injury group with 42 cases and renal function normal group with 38 cases according to the occurrence of early renal injury. The urinary Netrin-1, Kim-1, RBP and renal function indexes levels were compared between the two groups, and the correlation analysis was carried out. The influencing factors of early renal injury in HDCP were analyzed by Logistic regression. **Results:** The urinary Netrin-1 levels in normal pregnancy group, gestational hypertension group, mild preeclampsia group and severe preeclampsia group showed a gradually decreasing trend, while the urinary Kim-1 and RBP levels showed a gradually increasing trend, there were statistically significant differences in the pairwise comparison between multiple groups of data (all $P<0.05$). The urinary Netrin-1 level in renal function injury group was lower than that in renal function normal group, while the urinary Kim-1, RBP, blood urea nitrogen and

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serum creatinine and 24 h Urinary albumin excretion (UAE) levels in renal function injury group were significantly higher than those in renal function normal group (all P<0.05). According to Pearson correlation analysis, urinary Netrin-1 level was negatively correlated with blood urea nitrogen and serum creatinine, UAE in early renal injury in HDCP, while Kim-1, RBP levels were positively correlated with blood urea nitrogen and serum creatinine, UAE (all P<0.05). Logistic regression analysis showed that urinary Netrin-1 was a protective factor for early renal injury in HDCP, while Kim-1 and RBP were risk factors for early renal injury in HDCP (all P<0.05). **Conclusions:** With the decrease of urinary Netrin-1 level and the increase of Kim-1 and RBP levels, the risk of early renal injury in HDCP is higher, detection of urinary Netrin-1, Kim-1, RBP levels may be helpful to evaluate the severity of HDCP and renal function damage.

Key words: Hypertensive disorder complicating pregnancy; Urinary neurite guidance factor 1; Kidney injury molecule-1; Retinol binding protein; Influence factors

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前言

妊娠期高血压疾病（Hypertensive disorder complicating pregnancy，HDCP）属于妊娠期较为常见的一种疾病，主要临床表现包括高血压以及蛋白尿等，是导致孕产妇以及新生儿死亡的重要原因之一[1-3]。HDCP 发病时最早累及的器官往往是肾脏，长期处于高血压状态下会对孕妇以及胎儿的健康产生严重影响，甚至危及生命，早期及时发现 HDCP 肾功能损害，并开展相应治疗措施，可有效逆转肾功能[4,5]。由于 HDCP 合并肾功能损害时的临床症状较为隐匿，且不典型，临床医生往往难以作出准确的诊断，因此寻求一种有效诊断 HDCP 早期肾损伤的生物学指标显得尤为重要，亦是目前临床研究的热点。神经突起导向因子 1（Netrin-1）属于新型抗炎因子之一，于正常人尿液中低表达，而当出现急性肾损伤时，其在尿液中存在明显表达异常，是急性肾损伤早期诊断指标之一[6-8]。肾损伤分子 -1（Kidney injury molecule-1，Kim-1）是近年来所发现的一种新型肾脏损伤标记物，目前已被应用于肾脏损伤相关性疾病的诊断过程中[9,10]。视黄醇结合蛋白（Retinol binding protein，RBP）则是一类可运载维生素 A 的小分子结合蛋白，主要介导了细胞内视黄醇以及视黄酸的转运，和 HDCP 的发生、发展密切相关[11,12]。鉴于此，本文通过研究尿 Netrin-1、Kim-1、RBP 水平与 HDCP 早期肾损伤的关系，旨在为临床诊治提供靶点支持，现作以下报道。

1 对象与方法

1.1 一般资料

将我院从 2017 年 2 月～2020 年 2 月收治的 HDCP 患者 80 例纳入研究，年龄 21～38 岁，平均（25.83±3.42）岁；孕周 28～41 周，平均（31.31±2.19）周；HDCP 严重程度：妊娠期高血压 22 例，轻度子痫前期组 32 例、重度子痫前期组 26 例。另外随机选取同期于我院接受规律孕产检以及分娩正常妊娠孕妇 40 例作为正常妊娠组。年龄 21～37 岁，平均（26.91±3.36）岁；孕周 28～40 周，平均（32.09±2.06）周，HDCP 患者和正常妊娠组年龄、孕周比较差异无统计学差异（P>0.05），均衡可比。入选标准：（1）所有 HDCP 患者均符合 HDCP 相关诊断标准[13]；（2）均为单胎妊娠；（3）无临床病历资料的缺失；（4）所有患者均知情且签署同意书。剔除标准：（1）既往有高血压病史者；（2）合并糖尿病或甲状腺功能障碍者；（3）心、肝、肺等重要脏器发生严重病变者；（4）合并慢性感染或全身免疫性疾病者；（5）神志异常或合并神经系统疾病者。本研究与《赫尔辛基宣言》相关要求相符。

1.2 研究方法

（1）尿 Netrin-1、Kim-1、RBP 水平检测：分别采集所有受试者的清晨首次中段尿液 5 mL 左右，以 15cm 为离心半径，进行时长为 10 min 的 3000 r/min 离心处理，获取上清液，以酶联免疫吸附法完成相关检测，操作遵循试剂盒说明书完成，相关试剂盒购自博研生物科技有限公司。（2）肾功能指标水平检测：抽取受试者空腹静脉血 3 mL 检测血尿素氮、血肌酐水平，采集所有受试者的 24 h 尿液检测 24 h 尿白蛋白排出量（Urinary albumin excretion，UAE），采用脲酶法检测血尿素氮，采用苦味酸法检测血肌酐，相关试剂盒购自南京建成生物技术研究所；UAE 采用购自美国贝尔曼库尔特公司的 DU5800 生化仪及配套免疫透射比浊法试剂盒进行检测。（3）分组方式：将所有 HDCP 患者按照是否出现早期肾损伤分为肾功能损伤组 42 例和肾功能正常组 38 例，其中肾功能损伤判定标准为内生肌酐清除率（Creatinine clearance rate，Ccr）≥ 80 mL/min[14]。

1.3 统计学处理

数据处理软件为 SPSS 22.0，计量资料符合正态分布、方差齐性，以（$\bar{x}\pm s$）表示，两组比较采用 t 检验，多组之间的比较采用单因素方差分析，多组数据间两两对比采用 LSD-t 检验。Pearson 相关性分析 HDCP 早期肾损伤患者尿 Netrin-1、Kim-1、RBP 和肾功能指标水平的相关性，通过 Logistic 回归分析 HDCP 早期肾损伤的影响因素。P<0.05 预示差异有统计学意义。

2 结果

2.1 不同 HDCP 严重程度患者和正常妊娠组尿 Netrin-1、Kim-1、RBP 水平比较

正常妊娠组、妊娠期高血压组、轻度子痫前期组、重度子痫前期组尿 Netrin-1 水平呈逐渐降低趋势，而尿 Kim-1、RBP 水平均呈逐渐升高趋势，多组数据间两两对比差异均有统计学意义（均 P<0.05），见表 1。

2.2 肾功能损伤组和肾功能正常组患者尿 Netrin-1、Kim-1、RBP 以及肾功能指标水平比较

肾功能损伤组尿 Netrin-1 水平低于肾功能正常组，而尿 Kim-1、RBP 以及血尿素氮、血肌酐、UAE 水平均明显高于肾功能正常组（均 P<0.05），见表 2。

2.3 HDCP 早期肾损伤患者尿 Netrin-1、Kim-1、RBP 和肾功能

指标水平的相关性分析

经 Pearson 相关性分析可得：HDCP 早期肾损伤患者尿 Netrin-1 水平和血尿素氮、血肌酐、UAE 均呈负相关关系，而尿 Kim-1、RBP 水平和血尿素氮、血肌酐、UAE 均呈正相关（均 $P<0.05$），见表 3。

表 1 不同 HDCP 严重程度患者和正常妊娠组尿 Netrin-1、Kim-1、RBP 水平比较（$\bar{x}\pm s$）

Table 1 Comparison of urinary Netrin-1, Kim-1 and RBP levels between patients with different HDCP severity and normal pregnancy group（$\bar{x}\pm s$）

Groups	n	Netrin-1(μg/L)	Kim-1(μg/L)	RBP(mg/L)
Normal pregnancy group	40	213.23±20.59	5.27±1.34	0.62±0.14
Gestational hypertension group	22	174.67±17.52$^{\#}$	6.85±2.05$^{\#}$	1.37±0.35$^{\#}$
Mild preeclampsia group	32	139.38±14.56$^{\#*}$	8.42±2.46$^{\#*}$	1.62±0.39$^{\#*}$
Severe preeclampsia group	26	108.56±13.06$^{\#*¥}$	11.06±2.57$^{\#*¥}$	2.14±0.46$^{\#*¥}$
F	-	8.492	7.385	11.051
P	-	0.000	0.000	0.000

Note: compared with normal pregnancy group, $^{\#}P<0.05$; compared with gestational hypertension group, $^{*}P<0.05$; compared with mild preeclampsia group, $^{¥}P<0.05$.

表 2 肾功能损伤组和肾功能正常组患者尿 Netrin-1、Kim-1、RBP 以及肾功能指标水平比较（$\bar{x}\pm s$）

Table 2 Comparison of urinary Netrin-1, Kim-1, RBP and renal function indexes levels between renal function injury group and renal function normal group（$\bar{x}\pm s$）

Groups	n	Netrin-1(μg/L)	Kim-1(μg/L)	RBP(mg/L)	Urea nitrogen (mmol/L)	Creatinine (μmol/L)	UAE(mg/24h)
Renal function injury group	42	117.49±14.02	12.04±1.30	2.41±0.35	4.68±1.25	107.48±27.12	1164.38±231.82
Renal function normal group	38	181.21±20.83	6.48±1.06	1.18±0.24	3.31±0.89	68.39±9.26	172.96±43.18
t	-	16.187	20.831	18.141	5.593	8.447	25.944
P	-	0.000	0.000	0.000	0.000	0.000	0.000

表 3 HDCP 早期肾损伤患者尿 Netrin-1、Kim-1、RBP 和肾功能指标水平的相关性分析

Table 3 Correlation Analysis of urinary Netrin-1, Kim-1, RBP and renal function indexes levels in patients with early renal injury in HDCP

Indexes	Urea nitrogen		Creatinine		UAE	
	r	*P*	r	*P*	r	*P*
Netrin-1	-0.523	0.000	-0.411	0.000	-0.479	0.001
Kim-1	0.547	0.000	0.352	0.006	0.583	0.000
RBP	0.418	0.000	0.462	0.003	0.432	0.000

2.4 HDCP 早期肾损伤的 Logistic 回归分析

以 HDCP 早期肾损伤与否作为因变量，赋值如下：早期肾损伤 =1，无早期肾损伤 =0；以尿 Netrin-1、Kim-1、RBP 和肾功能指标水平为自变量，赋值均为原值输入。经 Logistic 回归分析发现：尿 Netrin-1 是 HDCP 早期肾损伤的保护因素，而尿Kim-1、RBP 是 HDCP 早期肾损伤的危险因素（均 $P<0.05$），见表 4。

表 4 HDCP 早期肾损伤的 Logistic 回归分析

Table 4 Logistic regression analysis of early renal injury in HDCP

Factors	β	S.E	Waldχ^2	OR	95%CI	*P*
Netrin-1	-0.583	0.305	4.832	0.539	0.321～0.894	0.012
Kim-1	0.432	0.205	5.932	1.405	1.052～1.683	0.001
RBP	0.418	0.155	7.395	1.692	1.130～1.835	0.000
Urea nitrogen	0.106	0.053	0.588	0.844	0.812～0.866	0.119
Creatinine	0.123	0.068	0.683	0.809	0.793～0.873	0.105
UAE	0.135	0.022	0.495	0.811	0.799～0.869	0.135

3 讨论

HDCP 是一种由多因素共同作用导致的疾病，发病时全身小血管痉挛以及收缩，继而导致周围血管阻力增大，全身器官灌注减少，最终导致器官脏器损伤的发生，其中又以肾脏损伤表现尤为明显，包括肾小球痉挛、肾血流动力学异常等，患者普遍存在不同程度的肾功能下降，进一步可能损害孕妇肾脏，甚至引发肾衰竭，严重威胁母婴生命健康安全[15-17]。故此，早期诊断 HDCP 肾损伤显得尤为重要，亦是改善母婴结局的重中之重。既往，临床上主要是通过血肌酐以及血尿素氮实现肾功能损伤的监测，然而，上述两项指标仅能间接反映肾小球滤过功能受损程度，且在一定程度上受肌肉量以及蛋白质摄入量的影响，和肾小球实际滤过功能存在一定误差[18-20]。因此，寻求 HDCP 早期肾功能损伤诊断的指标已然成为研究热点。

本研究发现：HDCP 早期肾损伤患者尿 Netrin-1 水平较低，而尿 Kim-1、RBP 水平较高，且与 HDCP 病情严重程度相关，Netrin-1 属于层黏连蛋白样分子，于多种组织中均有所表达，且和炎症密切相关，可促进损伤的肾小管上皮细胞增殖，同时发挥抑制细胞凋亡的作用，继而减少缺血再灌注引发的肾损伤，具有明显的肾脏保护作用[21-23]。Kim-1 在一般细胞中基本无表达，但在多种疾病导致的肾脏功能损害中，肾小管上皮细胞表面的尿 Kim-1 水平异常升高，其作为一种Ⅰ型跨膜蛋白，仅在肾损伤细胞中表达，因此可作为早期肾损伤的诊断指标[24-26]。RBP 主要是指源自肝脏合成，主要功能是将视黄醇转运至上皮细胞，正常状态下血液中 90%以上的 RBP 和甲状腺结合蛋白相结合，且无法被肾小球滤出，而少数游离的 RBP 往往于近曲小管被基本吸收，以此在尿液中的含量极少，而当肾脏发生损伤，可能引起尿液中的 RBP 水平异常升高，说明 RBP 可能是肾早期损伤的关键性指标之一。此外，HDCP 早期肾损伤患者尿 Netrin-1 水平和血尿素氮、血肌酐、UAE 均呈负相关关系，而 Kim-1、RBP 水平和血尿素氮、血肌酐、UAE 均呈正相关关系，究其原因可能在于尿 Netrin-1 水平的下降以及尿 Kim-1、RBP 水平的升高，在一定程度上反映了机体肾损伤程度的加剧，而血尿素氮、血肌酐、UAE 均是临床上应用较为广泛的评价肾功能的生物学指标，因此和尿 Netrin-1、Kim-1、RBP 水平密切相关，提示在临床实际工作中可能通过检测尿 Netrin-1、Kim-1、RBP 水平，继而达到评估 HDCP 早期肾损伤严重程度的目的。另外，Netrin-1 是 HDCP 早期肾损伤的保护因素，而 Kim-1、RBP 是 HDCP 早期肾损伤的危险因素，可能是 Netrin-1 主要是通过和其受体 UNC5B 相结合，从而促使胞内环磷酸腺苷含量的增加，同时减少趋化因子的分泌，抑制趋化作用导致的炎症细胞朝周围组织迁移，进一步有利于减轻脏器炎症反应，发挥保护作用。Kim-1 主要介导了血管内皮细胞损伤，凝血因子含量增多或活性增强，炎性细胞以及血小板活化、功能亢进，抗凝、纤溶因子含量减少或功能障碍，进一步促使止血、凝血以及抗凝系统的失衡，促进了肾损伤的发生。另有相关研究报道证实，尿 RBP 是 HDCP 早期肾脏损害的敏感指标。

综上所述，尿 Netrin-1、Kim-1、RBP 在 HDCP 早期肾损伤患者中均存在异常表达，有可能成为诊断该病的可靠生物学指标，值得临床重点关注。

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