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冠心病患者血清 HN、CTRP3 与血脂及病情严重程度的关系研究 *

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摘要 目的:分析血清抗凋亡多肽(HN)、补体 C1q 肿瘤坏死因子相关蛋白因子 3(CTRP3)与冠心病(CHD)患者血脂及病情严重程度的关系。**方法:**选取 2017 年 1 月至 2018 年 12 月期间西安医学院第二附属医院收治的 CHD 患者 360 例(CHD 组),另选取同期健康体检者 100 例作为对照组(NC 组),比较两组血清 HN、CTRP3、血脂水平及基线资料;根据 CHD 患者病变支数分为单支病变组(n=131)、双支病变组(n=119)、多支病变组(n=110),根据冠状动脉造影结果测定 Gensini 积分,采用 Pearson 相关分析 HN、CTRP3 与血脂及 Gensini 积分的相关性。**结果:**CHD 组患者吸烟史比例、收缩压、空腹血糖、总胆固醇(TC)、甘油三酯(TG)及低密度脂蛋白(LDL-C)水平均高于 NC 组($P<0.05$),血清 HN、CTRP3 和高密度脂蛋白(HDL-C)均低于 NC 组($P<0.05$);CHD 双支病变组和多支病变组患者吸烟史、空腹血糖、TC 水平以及 Gensini 积分均高于单支病变组,CTRP3 和 HDL-C 水平均低于单支病变组,多支病变组收缩压高于单支病变组,多支病变组吸烟史、空腹血糖和 Gensini 积分均高于双支病变组,且多支病变组 CTRP3 低于双支病变组(均 $P<0.05$);Pearson 相关分析结果显示:CHD 患者血清 HN 水平与 HDL-C 水平呈正相关性,CHD 患者血清 CTRP3 水平与 Gensini 积分呈负相关($P<0.05$)。**结论:**CHD 患者血清中 HN、CTRP3 水平均显著降低,HN 与 HDL-C 水平呈正相关,CTRP3 降低程度与 CHD 患者病情严重程度有关,临床可考虑将其作为评估 CHD 患者病情严重程度的辅助血清学指标。

关键词:冠心病;抗凋亡多肽;补体 C1q 肿瘤坏死因子相关蛋白因子 3;血脂;Gensini 积分;病情;相关性

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Studies on the Relationship between Serum HN, CTRP3 and Blood Lipid, Severity of Illness in Patients with Coronary Heart Disease*

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ABSTRACT Objective: To analyze the relationship between serum anti-apoptotic polypeptide (HN), C1q/TNF-related protein 3 (CTRP3) and blood lipid and severity of illness in patients with coronary heart disease. **Methods:** A total of 360 patients with CHD (CHD group) who were admitted to the Second Affiliated Hospital of Xi'an Medical University from January 2017 to December 2018 were selected, and 100 healthy subjects in the same period were selected as healthy control group (NC group), the serum HN, CTRP3, blood lipid and baseline data were compared between the two groups. CHD patients were divided into single-vessel lesion group (n=131), double-vessel lesion group (n=119) and multi-vessel lesion group (n=110) according to the number of lesion branches, Gensini score was measured according to the results of coronary angiography, Pearson correlation analysis was used to analyze the correlation between HN and CTRP3 and blood lipid and Gensini scores. **Results:** The proportion of smoking history, systolic blood pressure, fasting blood sugar, total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C) in CHD group were higher than those in NC group ($P<0.05$), while serum HN, CTRP3 and high density lipoprotein (HDL-C) were lower than those in NC group ($P<0.05$); The smoking history, fasting blood glucose, TC level and Gensini score in CHD double-vessel lesion group and multi-vessel lesion group were higher than those in single-vessel lesion group, and CTRP3 and HDL-C levels were lower than those in single-vessel lesion group. Systolic blood pressure in multi-vessel lesion group was higher than that in single-vessel lesion group, the smoking history, fasting blood sugar and Gensini score in multi-vessel lesion group were higher than those in double-vessel lesion group, and CTRP3 in multi-vessel lesion group was lower than that in double-vessel lesion group (all $P<0.05$). Pearson correlation analysis showed that serum HN level was positively correlated with HDL-C level in patients with CHD, and serum CTRP3 level was negatively correlated with Gensini scores in patients with CHD ($P<0.05$). **Conclusion:** The serum HN and CTRP3 levels are significantly decreased in patients with CHD. HN is positively correlated with HDL-C. The degree of CTRP3 reduction is related to the severity of illness in patients with CHD. It could be considered as an auxiliary serological index to evaluate the severity of illness in patients with CHD.

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Key words: Coronary heart disease; Anti-apoptotic polypeptide; C1q/TNF-related protein 3; Blood lipid; Gensini score; Severity of illness; Correlation

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前言

冠状动脉粥样硬化性心脏病简称冠心病 (Coronary heart disease, CHD), 是因各种因素参与冠状动脉粥样硬化引起冠状管腔狭窄或闭塞, 从而导致心肌细胞缺血缺氧、坏死、心脏结构或生理功能发生改变的一种疾病^[1]。CHD 不仅具有发病率高、致残率高以及病死率高的特点, 而且不同危险分层的 CHD 治疗策略和预后差别极大^[2]。因此研究 CHD 的危险因素、发病机理、病理生理学过程和防治等内容一直是当代医学研究的热点。抗凋亡多肽(Humanin, HN)是一种在多种组织中表达并具有抗氧化、抗凋亡、抗炎作用的分子^[3,4]。补体 C1q 肿瘤坏死因子相关蛋白因子 3(C1q/TNF-related protein 3, CTRP3)是最近报道的具有抗炎特性的肿瘤坏死因子相关蛋白家族的成员之一, 研究显示其可能参与 CHD、肥胖和糖尿病等疾病的病理生理学过程^[5,6]。脂质代谢异常是 CHD 最重要的独立危险因素之一, 总胆固醇 (Totalcholesterol, TC)、甘油三酯(Triglyceride, TG)、高密度脂蛋白(High density lipoprotein, HDL-C)及低密度脂蛋白(Low density lipoprotein, LDL-C)是临床上常用的血脂检测指标, 有循证医学证据表明降脂治疗可显著降低 CHD 的发生率及病死率^[7,8]。然而, 目前有关 CHD 患者血清 HN、CTRP3 与血脂及病情严重程度关系的报道较少。因此本研究通过探讨血清 HN、CTRP3 与血脂及病情严重程度关系, 以期临床防治 CHD 提供参考。

1 资料与方法

1.1 一般资料

选取我院 2017 年 1 月至 2018 年 12 月期间收治的 CHD 患者 360 例作为 CHD 组, 纳入标准: (1) CHD 患者的诊断参考《中国心血管病预防指南》的诊断标准^[9]; (2) 临床资料齐全者; (3) 既往无手术治疗史者。排除标准: (1) 严重心力衰竭者; (2) 合并恶性肿瘤、自身免疫性疾病者; (3) 严重肝肾功能不全者; (4) 妊娠及哺乳期妇女; (5) 认知障碍者。CHD 组根据狭窄病变累及血管范围分为单支病变组($n=131$, 1 支主要冠脉或分支的血管内径狭窄 $\geq 50\%$), 双支病变组($n=119$, 2 支主要冠脉或分支的血管内径狭窄 $\geq 50\%$), 多支病变组($n=110$, 3 支及以上主要冠脉或分支的血管内径狭窄 $\geq 50\%$), 另外选择同期健康体检者 100 例作为对照组 (NC 组), CHD 组与 NC 组在性别、年龄方面比较无差异 ($P>0.05$), 见表 1。本研究已获我院伦理委员会批准进行。

1.2 方法

(1) 收集所有受试者的临床资料, 包括年龄、性别、身高、体重、血压、吸烟史等一般资料, 计算体质量指数 (Body mass index, BMI), $BMI = \text{体重}(\text{kg}) / [\text{身高}(\text{m})]^2$; 若受试者每天吸烟 ≥ 1 支, 且连续吸烟超过 1 年, 或在诊断为 CHD 前戒烟时间不足半年, 则被视为吸烟者; (2) 冠状动脉造影: 所有患者均采用飞利浦

FD-20 数字血管机(DSA)进行经桡动脉或股动脉途径冠状动脉造影检查, 详细记录 CHD 患者病变支数及狭窄程度。采用 Gensini 评分^[10]对病情严重程度进行定量评估: 冠状动脉狭窄 1~25% 记为 1 分, 26%~50% 记为 2 分, 51%~75% 记为 4 分, 76%~90% 记为 8 分, 91%~99% 记为 16 分, 完全闭塞即狭窄程度为 100% 记为 32 分。不同狭窄冠状动脉节段按 Gensini 评分标准乘以相应系数, 各分支得分之和即为患者最终评分; (3) 检测指标: 于体检者体检当日、患者入院次日抽取空腹外周静脉血 5 mL, 离心半径为 10 cm, 转速 3000 r/min 离心 5 min, 取上清置于 -20℃ 冰箱保存备用。采用酶联免疫吸附试验 (Enzyme linked immunosorbent assay, ELISA), 应用贝克曼 AU5800 全自动生化分析仪检测血清 HN、CTRP3、TC、TG、LDL-C、HDL-C 水平, 采用葡萄糖氧化酶法检测受试者空腹血糖水平, 试剂盒均购自上海朗顿公司, 操作严格按照说明书进行。

1.3 统计学方法

采用 SPSS23.0 统计分析软件进行数据分析, 符合正态分布的计量资料用 $\bar{x} \pm s$ 表示, 两组间比较采用 t 检验, 多组间比较采用单因素方差分析, 计数资料以 % 表示, 组间比较采用卡方检验; 应用 Pearson 相关分析各指标的相关性; 检验水准设为 $\alpha=0.05$ 。

2 结果

2.1 CHD 组与 NC 组基线资料、血清 HN、CTRP3 与血脂比较

CHD 组吸烟史比例、收缩压、空腹血糖、TC、TG、LDL-C 水平均高于 NC 组, HN、CTRP3 以及 HDL-C 水平均低于 NC 组 (均 $P<0.05$), 见表 1。

2.2 CHD 不同冠脉病变支数组基线资料、血清 HN、CTRP3 及血脂比较

双支病变组和多支病变组吸烟史比例、空腹血糖、TC 水平以及 Gensini 积分均高于单支病变组, CTRP3、HDL-C 水平均低于单支病变组, 多支病变组 CTRP3 低于双支病变组, 多支病变组收缩压高于单支病变组, 多支病变组吸烟史比例、空腹血糖和 Gensini 积分均高于双支病变组, 差异均有统计学意义 (均 $P<0.05$), 见表 2。

2.3 CHD 患者血清 HN、CTRP3 水平与血脂及 Gensini 积分的相关性

Pearson 相关分析结果显示: CHD 组患者血清 HN 水平与 HDL-C 水平呈正相关性 ($P<0.05$), 而与 TC、TG、LDL-C 及 Gensini 积分无相关性 (均 $P>0.05$); CHD 组患者血清 CTRP3 水平与 Gensini 积分呈负相关性 ($P<0.05$), 而与 TC、TG、HDL-C 及 LDL-C 无相关性 (均 $P>0.05$), 见表 3。

3 讨论

CHD 是全球发病率和死亡率较高的主要疾病, 是严重威胁人类身心健康的重大公共卫生问题^[11,12]。目前已确认 CHD 的

表 1 CHD 组与 NC 组基线资料、血清 HN、CTRP3 与血脂比较

Table 1 Comparison of baseline data, serum HN, CTRP3 and lipids between CHD group and NC group

Indexes	NC group(n=100)	CHD group(n=360)	t / χ^2	P
Male [n(%)]	60(60.00)	248(68.89)	2.795	0.095
Age(years)	65.12±6.83	65.46±8.65	-0.363	0.717
BMI(kg/m ²)	23.84±0.43	23.93±0.40	-1.805	0.072
Smoking history [n(%)]	24(24.00)	159(44.17)	13.143	0.000
Systolic blood pressure(mmHg)	125.25±8.04	146.36±15.91	-18.134	0.000
Diastolic blood pressure(mmHg)	76.62±7.79	77.65±7.12	-1.260	0.208
Fasting blood sugar(mmol/L)	5.50±0.43	7.14±0.77	-27.550	0.000
HN(ng/mL)	3.66±0.40	2.29±0.98	21.063	0.000
CTRP3(pg/mL)	74.14±14.52	58.69±3.55	15.025	0.000
TC(mmol/L)	2.02±0.92	2.21±0.80	-1.624	0.042
TG(mmol/L)	1.46±0.98	1.76±0.69	-2.839	0.005
HDL-C(mmol/L)	1.42±0.17	1.05±0.24	13.631	0.000
LDL-C(mmol/L)	2.60±0.68	3.02±0.89	-3.965	0.000

表 2 CHD 不同冠脉病变支数组基线资料、血清 HN、CTRP3 及血脂比较

Table 2 Comparison of baseline data, serum HN, CTRP3 and blood lipids in different CHD groups

Indexes	Single-vessel lesion group(n=131)	Double-vessel lesion group(n=119)	Multi-vessel lesion group (n=110)	F / χ^2	P
Male [n(%)]	84(64.12)	83(69.75)	81(73.64)	2.917	0.110
Age(years)	64.14±10.35	66.47±5.45	65.94±5.58	1.553	0.262
BMI(kg/m ²)	23.01±1.01	23.54±0.62	24.57±1.04	1.855	0.319
Smoking history [n(%)]	45(34.35)	49(41.18) ^a	65(59.09) ^{ab}	29.368	0.000
Systolic blood pressure(mmHg)	142.72±12.77	146.46±16.11	150.58±17.84 ^a	7.588	0.001
Diastolic blood pressure(mmHg)	77.02±8.59	77.69±5.62	78.36±6.54	1.057	0.348
Fasting blood sugar(mmol/L)	6.74±0.68	7.18±0.70 ^a	7.57±0.71 ^{ab}	42.366	0.000
HN(ng/mL)	2.44±0.93	2.19±0.95	2.22±1.03	2.549	0.080
CTRP3(pg/mL)	75.89±9.71	51.93±4.93 ^a	45.10±3.42 ^{ab}	736.805	0.000
TC(mmol/L)	2.01±0.90	2.18±0.56 ^a	2.48±0.76 ^a	0.363	0.032
TG(mmol/L)	1.72±0.85	1.74±0.71	1.82±0.77	0.587	0.556
HDL-C(mmol/L)	1.10±0.18	1.02±0.24 ^a	1.01±0.28 ^a	4.969	0.007
LDL-C(mmol/L)	2.98±0.76	3.04±0.98	3.03±0.90	0.857	0.425
Gensini score(scores)	33.65±15.19	42.50±13.80 ^a	60.72±15.38 ^{ab}	101.775	0.000

Note: compared with single-vessel lesion group, ^aP<0.05; compared with double-vessel lesion group, ^bP<0.05.

危险因素大概有 300 余种^[13],包括性别、年龄、CHD 家族史等不可干预因素,以及饮食、吸烟、高血脂、高血压、糖尿病等可干预因素^[14,15]。Gensini 评分是目前常用的一种评估冠状动脉病变程度的简单有效方法,常用于探究各种检测指标与冠脉病变程度相关性,冠状动脉狭窄程度越重,Gensini 积分越大,因此 Gensini 积分可准确地反映冠状动脉病变严重程度^[16,17]。

近年来研究显示 HN 具有保护神经、抗氧化、抗炎等生物学功能,还参与细胞保护、调节糖脂代谢、延缓动脉粥样硬化、防治 CHD 等心血管疾病的病理生理学过程^[18,19]。Widmer RJ

等^[20]研究显示,非 CHD 人群血清中 HN 水平显著高于 CHD 患者,Lee C 等^[21]报道了 HN 具有治疗心肌缺血再灌注损伤作用。本研究结果显示,与 NC 组相比,CHD 组患者血清 HN 水平显著降低,但是不同冠脉病变支数组间检测到 HN 水平无统计学差异,推测 HN 并不能很好地反映冠状动脉病变严重程度;进一步采用 Pearson 相关性分析,结果提示 CHD 组患者血清中 HN 与 HDL-C 水平呈正相关,而与 TC、TG、LDL-C 及 Gensini 积分无相关性,说明 HN 可能是 CHD 的潜在保护因素。胡淑鸿等^[22]的研究显示 HN 可降低病理条件下高脂血症小鼠模型的

表 3 血清 HN、CTRP3 与血脂及 Gensini 积分的相关性分析

Table 3 Correlation Analysis of serum HN, CTRP3, blood lipid and Gensini score

Indexes	HN		CTRP3	
	r	P	r	P
TC	-0.067	0.795	-0.076	0.750
TG	-0.077	0.774	-0.063	0.733
HDL-C	0.722	0.031	0.592	0.082
LDL-C	-0.043	0.808	-0.014	0.848
Gensini score	-0.062	0.821	-0.513	0.043

血脂水平,提示 HN 可能通过降低血脂来影响心血管疾病的发生发展。CTRP3 是最近发现的具有调节糖脂代谢作用的脂肪因子,与脂联素同源,参与抗炎、抗凋亡、促进血管新生以及减轻心肌重构等重要生理病理学过程^[23]。CTRP3 可通过抑制三酰甘油合成酶的表达从而降低肝脏三酰甘油含量,进而减弱高脂饮食诱导的肝细胞脂肪变性,并参与高血压、高血脂、糖尿病、CHD 等心血管及代谢性疾病的发生发展^[24,25]。Zhang CL 等^[26]研究显示 CTRP3 通过 AMPK/PGC-1 α 信号途径促进心肌细胞线粒体生物合成,并充当心肌细胞缺血缺氧性损伤保护因子,提示 CTRP3 可能是线粒体生物合成的内源调节剂。Yi W 等^[27]动物实验表明外源性 CTRP3 能够显著增加 Akt 磷酸化、缺氧诱导因子-1 和血管内皮生长因子的表达从而促进血管新生,该研究证明 CTRP3 是一种新型的具有抗凋亡、促血管生成和心脏保护功能的脂肪因子,其有望成为减少心肌缺血后心脏重构,改善心脏功能新的治疗靶点。Choi KM 等^[28]的临床试验显示,与健康对照组相比,急性冠脉综合征和稳定型心绞痛患者血清中的 CTRP3 水平显著降低。既往研究显示 CHD 患者的循环 CTRP3 浓度明显降低,且循环中较低水平的 CTRP3 是 CHD 和 2 型糖尿病的危险因素^[29,30],本研究结果提示,与非 CHD 受试者比较,CHD 组患者血清中 CTRP3 水平显著减少,CHD 组中双支和多支冠脉病变组血清 CTRP3 水平均较单支病变组低,并且 CTRP3 水平与 Gensini 积分呈负相关,提示 CTRP3 与 CHD 患者疾病严重程度有关。

综上所述,CHD 患者的血清中 HN、CTRP3 水平均显著降低,HN 与 HDL-C 水平呈正相关,CTRP3 降低程度与 CHD 患者病情严重程度有关,临床可考虑将其作为评估 CHD 患者病情严重程度的辅助血清学指标。

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