

doi: 10.13241/j.cnki.pmb.2017.32.017

血清 HCY、MMP-9、NT-proBNP 水平与老年 2 型糖尿病大血管病变的相关性研究 *

周文锐 朱敏洁[△] 李琛 梁兴伦 董迪夷

(同济大学附属杨浦医院 老年科 上海 200090)

摘要 目的:探讨血清同型半胱氨酸(HCY)、金属蛋白酶 9(MMP-9)、N-端 B 型钠利尿肽(NT-proBNP)变化与老年 2 型糖尿病大血管病变的关系。**方法:**选取我院 2014 年 5 月至 2016 年 5 月收治的老年 2 型糖尿病患者 50 例,依据大血管病变发生情况将其分为合并大血管病变组(A 组, n=25)和未合并大血管病变组(B 组, n=25),另选取同期来我院进行体检的健康人员 50 例作为对照组,比较三组的一般临床资料、血清 HCY、MMP-9、NT-proBNP 水平。**结果:**A 组患者的收缩压、舒张压、空腹血糖(FBG)、餐后 2h 血糖(2hBG)水平均显著高于 B 组($P<0.05$),高密度脂蛋白胆固醇(HDL-C)水平显著低于 B 组($P<0.05$),但三组患者的性别、年龄、体质指数(BMI)、糖化血红蛋白(HbA1c)、总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)水平比较差异均无统计学意义($P>0.05$)。A 组、B 组患者的 BMI、收缩压、舒张压、FBG、2hBG、HbA1c、TG、LDL-C 水平均显著高于对照组($P<0.05$), LDL-C 水平均显著低于对照组 ($P<0.05$), 但三组人员的性别、年龄比较差异均无统计学意义 ($P>0.05$)。A 组患者的血清 HCY、MMP-9、NT-proBNP 水平均显著高于 B 组($P<0.05$); A 组、B 组患者的 HCY、MMP-9、NT-proBNP 水平均显著高于对照组($P<0.05$)。**结论:**血清 HCY、MMP-9、NT-proBNP 水平与老年 2 型糖尿病的大血管病变显著相关。

关键词:老年 2 型糖尿病; 同型半胱氨酸(HCY); 金属蛋白酶 9(MMP-9); N-端 B 型钠利尿肽(NT-proBNP); 大血管病变

中图分类号: R587.2; R543 **文献标识码:** A **文章编号:** 1673-6273(2017)32-6283-04

Relationships between serum HCY, MMP-9, NT-proBNP Levels and Large Vascular Disease of Elderly patients with Type 2 Diabetes Mellitus*

ZHOU Wen-rui, ZHU Min-jie[△], LI Chen, LIANG Xing-lun, DONG Di-yi

(Affiliated Yangpu hospital, Tongji University, Shanghai, 200090, China)

ABSTRACT Objective: To investigate the relationships between serum Homocysteine (HCY), metalloproteinase 9 (MMP-9), N-terminal B type natriuretic peptide (NT-proBNP) levels and the large vascular disease of elderly type 2 diabetes mellitus. **Methods:** 50 cases of elderly patients with type 2 diabetes mellitus in our hospital from May 2014 to May 2016 were selected and divided into the macrovascular disease group (A group, n=25) and the macrovascular disease group (B group, n=25) according to incidence of vascular disease. These patients were regarded as the diabetes group, another 50 cases of healthy controls in our hospital for physical examination in the same period were selected as the control group, the clinical data, HCY, MMP-9, NT-proBNP levels of the three groups were statistically analyzed. **Results:** In the diabetic group, the systolic and diastolic blood pressures, Fasting plasma glucose (FBG), postprandial 2H blood glucose (2hBG) of A group were significantly higher than B group ($P<0.05$), the High density lipoprotein cholesterol (HDL-C) level was significantly lower than B group ($P<0.05$), but the differences of genders, ages, Body mass index (BMI), glycosylated hemoglobin (HbA1c), total cholesterol (TC), three acyl glycerol (TG), low density lipoprotein cholesterol (LDL-C) levels between the three groups had no statistical significance ($P>0.05$); In the diabetes group, the BMI, systolic blood pressure and diastolic blood pressure, FBG, 2hBG, HbA1c, TG, TG and LDL-C of A group, B group were significantly higher than the control group ($P<0.05$), the LDL-C levels were significantly lower than the control group ($P<0.05$), but the differences of sexes and ages between the three groups had no statistical significance ($P>0.05$); The HCY, MMP-9, NT-proBNP levels of the A group in the diabetic group was significantly higher than the B group ($P<0.05$), the HCY, MMP-9 and NT-proBNP levels of the A group and B group were significantly higher than the control group ($P<0.05$). **Conclusion:** The serum HCY, MMP-9, NT-proBNP levels were significantly correlated with the large vascular disease of elderly patients with type 2 diabetes mellitus.

Key words: Elderly type 2 diabetes mellitus; HCY; MMP-9; NT-proBNP; Large vascular disease

Chinese Library Classification(CLC): R587.2; R543 **Document code:** A

Article ID: 1673-6273(2017)32-6283-04

* 基金项目: 同济大学附属杨浦医院院级课题支持项目(Se1201418)

作者简介: 周文锐(1980-), 女, 主治医师, 硕士, 研究方向: 糖尿病及其慢性并发症, E-mail: wenrui_1999@163.com

[△] 通讯作者: 朱敏洁, 副主任医师, 主要研究方向: 老年疾病, E-mail: shypzhouwenrui@163.com

(收稿日期: 2017-03-30 接受日期: 2017-04-23)

糖尿病是以高血糖为特征的代谢紊乱性疾病,大血管病变是糖尿病患者致残和早亡的主要原因。胰岛素抵抗(IR)、脂质代谢紊乱、内皮功能障碍等都是糖尿病大血管病变的主要发病机制,最近研究表明血清 HCY、MMP-9、NT-proBNP 可能在其发生发展中起着重要作用^[1]。本研究采取随机、对照设计,探讨 HCY、MMP-9、NT-proBNP 指标水平在对照组与 2 型糖尿病伴颈动脉硬化患者组之间有无显著性差异,内容及结果。本研究将阐述 HCY、MMP-9、NT-proBNP 变化与老年 2 型糖尿病患者大血管病变的相关性,为测定血清 HCY、MMP-6、BNP 临床应用提供理论依据,发挥更强的靶器官保护作用,为治疗糖尿病大血管并发症提供了有力的武器,现报道如下。

1 资料与方法

1.1 一般资料

选取我院 2014 年 5 月至 2016 年 5 月收治的老年 2 型糖尿病患者 50 例作为糖尿病组,所有患者均符合 WHO1999 年制定的 2 型糖尿病诊断标准^[2],均知情同意;将有肝肾疾病等患者排除在外。其中,男性 27 例,女性 23 例,年龄 65-85 岁,平均(75.3±10.2)岁。依据大血管病变发生情况将这些患者分为合并大血管病变组(A 组,n=25)和未合并大血管病变组(B 组,n=25)三组。另选取同期来我院进行体检的健康人员 50 例作为对照组,其中男性 25 例,女性 25 例,年龄 65-85 岁,平均(75.8±10.0)岁。三组人员的一般资料比较差异均无统计学意义(P>0.05),具有可比性。

1.2 方法

1.2.1 临床资料的收集 将三组人员的性别、年龄、体质量指

数(BMI)、血压、病程、血尿生化数据[血清总胆固醇(TC)、三酰甘油(TG)、低密度脂蛋白胆固醇(LDL-C)、高密度脂蛋白胆固醇(HDL-C)]、空腹血糖(FBG)、餐后 2 h 血糖(2hBG)、糖化血红蛋白(HbA1c)、心电图等临床资料收集起来。

1.2.2 血清 HCY、MMP-9、NT-proBNP 水平的检测 患者入院第 1~2 天病情未经控制条件下和健康体检者清晨卧位抽取静脉血 10 mL,采取低温离心,分离血浆置 -20 ℃冰箱内储存备测。严格按照说明书操作采用酶联免疫吸附法检测血浆同型半胱氨酸(HCY)、金属蛋白酶 9(MMP-9)、N-端 B 型钠利尿肽(NT-proBNP)水平。

1.3 统计学处理

采用 SPSS 13.0 进行统计,正态分布数据以($\bar{x} \pm s$)表示,差异比较用 t 检验,以 P<0.05 为差异具有统计学意义。

2 结果

2.1 三组人员的临床资料比较

糖尿病组中 A 组患者的收缩压、舒张压、FBG、2hBG 均显著高于 B 组(P<0.05),HDL-C 水平显著低于 B 组(P<0.05),但三组患者的性别、年龄、BMI、HbA1c、TG、TG、LDL-C 水平之间的差异均无统计学意义(P>0.05);糖尿病组中 A 组、B 组患者的 BMI、收缩压、舒张压、FBG、2hBG、HbA1c、TG、TG、LDL-C 水平均显著高于对照组(P<0.05),LDL-C 水平均显著低于对照组(P<0.05),但三组人员的性别、年龄之间的差异均无统计学意义(P>0.05),Logistics 回归分析结果表明,老年 2 型糖尿病患者大血管病变的危险因素为高血压、高血糖。具体见表 1。

表 1 三组人员的临床资料比较

Table 1 Comparison of the clinical data among three groups

Projects	Classification	Diabetes group(n=50)	Control group(n=50)	
			Group A (n=25)	Group B(n=25)
Gender	Male	14(56.0)	13(52.0)	25(50.0)
	Female	11(44.0)	12(48.0)	25(50.0)
Age (years old)		75.3±10.2	75.3±10.2	75.8±10.0
BMI(kg/m ²)		27.6±3.8*	26.1±3.8*	21.4±3.1
Blood pressure (mmHg)	Systolic pressure	155.3±22.7**	145.9±22.1*	138.9±21.4
	Diastolic pressure	81.4±12.1**	77.8±11.0*	74.1±9.4
Blood glucose (mmol/L)	FBG	10.4±2.8**	9.0±3.0*	5.1±0.8
	2hBG	16.4±5.7**	12.6±5.0*	4.2±1.1
	HbA1c	8.8±1.4*	8.6±1.6*	4.5±1.3
Biochemical index (mmol/L)	TC	5.9±1.2*	5.7±1.2*	3.8±0.9
	TG	2.9±1.2*	2.5±1.4*	1.5±0.9
	LDL-C	4.2±1.2*	3.8±1.3*	2.5±1.7
	HDL-C	0.8±0.3**	1.0±0.4*	1.3±0.6

Note: Compared with B group in the same group *P<0.05; Compared with control group, *P<0.05.

2.2 三组血清 HCY、MMP-9、NT-proBNP 水平比较

糖尿病组中 A 组患者的 HCY、MMP-9、NT-proBNP 水平

均显著高于 B 组(P<0.05);A 组、B 组患者的 HCY、MMP-9、NT-proBNP 水平均显著高于对照组(P<0.05),具体见表 2。

表 2 三组血清 HCY、MMP-9、NT-proBNP 水平的比较($\bar{x} \pm s$)Table 2 Comparison of the serum HCY, MMP-9 and NT-proBNP levels between three groups($\bar{x} \pm s$)

Projects	Diabetes group(n=50)		Control group(n=50)
	group A(n=25)	group B(n=25)	
HCY($\mu\text{mol/L}$)	20.1 $\pm$ 9.5**	12.2 $\pm$ 6.4*	9.6 $\pm$ 4.1
MMP-9(ng/ml)	251.5 $\pm$ 21.3**	193.5 $\pm$ 26.0*	120.2 $\pm$ 15.5
NT-proBNP(pg/ml)	181.0 $\pm$ 10.5**	99.3 $\pm$ 10.2*	82.0 $\pm$ 10.4

Note: Compared with B group in the same group **P<0.05; Compared with control group, *P<0.05.

3 讨论

HCY 是甲硫氨酸代谢的中间产物,影响血中 HCY 水平最主要的因素是叶酸、VitB12、VitB6 缺乏。目前认为高 HCY 血症是动脉粥样硬化的一个独立危险因素^[3],体内外实验结果表明血管内皮细胞在 HCY 的作用下会直接受到损伤,血管功能也会在 HCY 的作用下直接发生异常,进而引发内皮细胞衰老,增加自由基产生,降低一氧化氮(NO)活性或表达,增加血管性血友病因子(vWF)等分泌,从而扰乱血液凝血及纤溶功能,造成血管硬化及血栓形成^[4]。HCY 对糖尿病患者内皮功能造成影响的途径为氧化应激系统,能够为修饰低密度脂蛋白系统提供良好的前提条件,促进动脉粥样硬化病变的加重。

很多细胞因子及酶活性也会糖尿病大血管病变的发生发展造成一定程度的影响,其中在细胞外基质代谢中,基质金属蛋白酶(MMPs)及其组织抑制因子(TIMPs)占有极为重要的地位。而在基质金属蛋白酶家族中,MMP-9 占有极为重要的地位,其能够促进基底膜胶原的降解,在中膜平滑肌细胞增生迁移、从基底膜屏障及内膜弹力层穿过过程中发挥着必不可少的作用,在动脉粥样硬化(AS)形成及内膜损伤反应过程中也发挥着极为重要的作用^[5]。

NT-proBNP 是一种由心室肌细胞分泌的具有利尿,利钠,扩张血管作用激素类物质。常在心室负荷过重或扩大时分泌增加,因而能反映心室的功能状态,NT-proBNP 与左心室射血分数水平密切相关,可在对心力衰竭患者病情程度、疗效及预后的判断中应用^[6]。现阶段,临床普遍认为^[7],对 NT-proBNP 进行刺激使其释放的另一个重要因素为心肌缺血,由于冠心病患者冠状动脉一定程度狭窄及缺乏充足的供血,因此造成心肌细胞将 NT-proBNP 分泌出来。2 型糖尿病患者心力衰竭等意外事件的发生率随着其 BNP 浓度的提升而提升,进而提升其 10 年冠心病发病危险性,降低其生存率。因此,在早期诊断、治疗老年 2 型糖尿病合并冠心病及心衰患者及对其药物副作用进行监测、判断其预后的过程中,测定血清 BNP 水平具有重要的临床意义。

相关医学学者认为^[8],HCY 能够协同糖基化终末产物,使血管内皮在糖基化终末产物中暴露,进而损伤内皮。Fonseca 等^[9-12]还认为,不同程度的糖尿病代谢紊乱可能和高 HCY 血症相互作用,为动脉粥样硬化的发生发展提供良好的前提条件,虽然现阶段临床还没有完全弄清楚糖尿病动脉粥样硬化中高 HCY 的机制,但是大部分相关医学学者认为^[13-15],糖尿病心血管疾病的一个极为重要的危险因素就是高 HCY。多项相关医

学研究均显示^[6-18],和非糖尿病患者相比,糖尿病患者具有更不稳定的动脉粥样斑块,而和 AS 患者相比,2 型糖尿病合并 AS 病变患者具有显著较高的 MMP-9 水平^[19-25]。研究发现^[26-28],颈动脉硬化严重程度与冠状病变密切相关,糖尿病合并颈动脉硬化患者可能有心肌缺血存在,损伤心肌功能,增加室壁张力,增多心肌细胞对 NT-proBNP 的释放。本研究结果表明,糖尿病组中 A 组患者的 HCY、MMP-9、NT-proBNP 水平均显著高于 B 组(P<0.05);A 组、B 组患者的 HCY、MMP-9、NT-proBNP 水平均显著高于对照组(P<0.05),和上述相关医学研究结果一致。导致 2 型糖尿病合并 AS 患者血中 MMP-9 含量增高的可能原因为:(1)氧化应激状态,在高血糖环境下,葡萄糖和糖基化终末产物自动氧化、多元醇旁路活化,可产生大量的氧自由基和超氧化物阴离子;(2)2 型糖尿病就是一种慢性炎症状态。

总之,老年 2 型糖尿病患者的血清 HCY、MMP-9、NT-proBNP 水平与大血管病变显著相关。

参考文献(References)

- [1] 侯亚利,刘永铭,马苏美,等. 2 型糖尿病患者心脏功能变化的研究[J].中国糖尿病杂志, 2011, 19(11): 834-837
Hou Ya-li, Liu Yong-ming, Ma Su, et al. Study on the changes of cardiac function in patients with type 2 diabetes[J]. Chinese Journal of diabetes, 2011, 19(11): 834-837
- [2] 王青,刘卫红,冷峰. BNP 在糖尿病肾病患者血浆中的变化[J].大连医科大学学报, 2008, 30(3): 271-272
Wang Qing, Liu Weihong, Leng Feng. BNP in plasma of patients with diabetic nephropathy [J]. Journal of Dalian Medical University, 2008, 30 (3): 271-272
- [3] 董雪红,李连喜,梁文昌,等. 2 型糖尿病人微血管舒张功能测定及其影响因素分析[J].中国病理生理杂志, 2007, 23(5): 893-896
Dong Xue-hong, Li Lian-xi, Liang Wen-chang, et al. Measurement of micro vascular diastolic function and its influencing factors in patients with type.2 diabetes [J]. Journal of the Chinese Journal of pathophysiology, 2007, 23(5): 893-896
- [4] 李连喜,陶征,陈霞,等. 2 型糖尿病血管病变时血浆 ANP、BNP 及 CNP 的变化及临床意义[J].中国病理生理杂志, 2008, 24(2): 350-353
Li Lian-xi, Tao Zheng, Chen Xia, et al. Changes and clinical implications of plasma ANP, BNP and CNP levels in type 2 diabetic patients with vascular complications [J]. Chinese Journal of pathophysiology, 2008, 24(2): 350-353
- [5] 贾春文,秦晓同,景宏美.利钠肽系统与心血管疾病的关系[J].南通大学学报(医学版), 2006, 26(5): 397-399
Jia Chun-wen, Qin Xiao-tong, Jing Hong-mei. The relationship

- between [J]. Natriuretic peptide system and cardiovascular disease Journal of Nantong University (Medical Science Edition), 2006, 26 (5): 397-399
- [6] 邹丽伟. 糖尿病患者颈动脉粥样硬化的超声检测[J]. 中国超声杂志, 2005, 4(17): 525-526
- Zou Li-wei. Ultrasonic detection of carotid atherosclerosis in diabetic patients[J]. Chinese Journal of ultrasound, 2005, 4(17): 525-526
- [7] 朱雪明, 沈海英, 冯萍, 等. 血浆脑钠素和心钠素在心力衰竭中的诊断价值及评价[J]. 中华检验医学杂志, 2006, 29(10): 923-925
- Zhu Xue-ming, Shen Hai-ying, Feng Ping, et al. The value of plasma brain natriuretic peptide and atrial natriuretic peptide in diagnosis of heart failure and evaluation [J]. Chinese medical journal, 2006, 29 (10): 923-925
- [8] 于鹏, 于华. 超声监测颈动脉粥样硬化与冠心病的相关性分析[J]. 实用诊断与治疗杂志, 2007, 21(21): 934-935
- Yu Peng, Yu Hua. Correlation analysis of carotid artery atherosclerosis and coronary artery disease by ultrasonic monitoring [J]. Journal of practical diagnosis and treatment, 2007, 21(21): 934-935
- [9] Zefeng Xia, Geng Wang, Huiqing Li, et al. Influence of Bariatric Surgery on the Expression of Nesfatin-1 in Rats with Type 2 Diabetes Mellitus[J]. Current Pharmaceutical Design, 2015, 21(11): 1464-1471
- [10] Nikhil S, Sahajpal, Subheet K. Jain. Molecular Remodeling of the Insulin Receptor Pathway by Thiazolidinediones in Type 2 Diabetes Mellitus: A Brief Review [J]. Protein & Peptide Letters, 2016, 23(9): 836-847
- [11] Raza ST, Abbas S, Ahmad A, et al. Association of Glutathione-S-Transferase (GSTM1 and GSTT1) and FTO Gene Polymorphisms with Type 2 Diabetes Mellitus Cases in Northern India [J]. Balkan Journal of Medical Genetics, 2014, 17(1): 47-54
- [12] D Popović, J Nikolajević Starčević, M Šantl Letonja, et al. PECAM-1 gene polymorphism (rs668) and subclinical markers of carotid atherosclerosis in patients with type 2 diabetes mellitus[J]. Balkan Journal of Medical Genetics, 2016, 19(1): 63-70
- [13] I V Kologrivova, T E Suslova, O A Koshel'skaya, et al. System of Matrix Metalloproteinases and Cytokine Secretion in Type 2 Diabetes Mellitus and Impaired Carbohydrate Tolerance Associated with Arterial Hypertension [J]. Bulletin of Experimental Biology and Medicine, 2014, 156 (5): 635-638
- [14] S Karachanak-Yankova, R Dimova, D. Nikolova, et al. Epigenetic Alterations in Patients with Type 2 Diabetes Mellitus [J]. Balkan Journal of Medical Genetics, 2015, 18 (2): 15-24
- [15] S Merlo, J Novák, N. Tkáčová, et al. Association of the ACE rs4646994 AND rs4341 Polymorphisms with the Progression of Carotid Atherosclerosis in Slovenian Patients with Type 2 Diabetes Mellitus[J]. Balkan Journal of Medical Genetics, 2015, 18(2): 37-42
- [16] Chunxia Wang, Kailiang Fu, Huaijun Liu, et al. Brain structural changes and their correlation with vascular disease in type 2 diabetes mellitus patients: a voxel-based morphometric study [J]. Neural Regeneration Research, 2014, 9 (16): 1548-1556
- [17] Francieli Rohden, Cintia S. Costa, Thais O. Hammes, et al. Obesity Associated with Type 2 Diabetes Mellitus Is Linked to Decreased PC1/3 mRNA Expression in the Jejunum [J]. Obesity Surgery, 2014, 24(12): 2075-2081
- [18] Atanas G. Baltadjiev, Stefka V. Vladeva. Clinical Investigations: Correlations Between Human Somatotype Components And Some Anthropometric Parameters In Male Patients with Type 2 Diabetes Mellitus[J]. Folia Medica, 2014, 56(3): 175-181
- [19] H Gill, S Yadav, V Ramesh, et al. A prospective study of prevalence and association of peripheral neuropathy in Indian patients with newly diagnosed type 2 diabetes mellitus [J]. Journal of Postgraduate Medicine, 2014, 60 (3): 270-275
- [20] Jin Li, Guangwei Xie, Qingzhong Tian, et al. Laparoscopic jejunoileal side-to-side anastomosis for the treatment of type 2 diabetes mellitus in Chinese patients with a body mass index of 24-32 kg/m² [J]. Journal of Cancer Research and Therapeutics, 2016, 12 (5): 5-10
- [21] Fei Pei, Jian Sun. New Insight into Improvement of Cardiovascular Outcomes with Intensive Glycemic Control in Patients with Metabolic Syndrome and Type 2 Diabetes Mellitus Included[J]. Cell Biochemistry and Biophysics, 2015, 71(1): 9-15
- [22] A-ping Sun, Lu Tang, Qin Liao, et al. Coexistent Charcot-Marie-Tooth type 1A and type 2 diabetes mellitus neuropathies in a Chinese family[J]. Neural Regeneration Research, 2015, 10(10): 1696-1699
- [23] Omer Akhter, Faraz Fiazuddin, Ayesha Shaheryar, et al. Central adiposity is significantly higher in female compared to male in Pakistani type 2 diabetes mellitus patients [J]. Indian Journal of Endocrinology and Metabolism, 2015, 19(1): 72-76
- [24] Oyewole Emmanuel, Agofure Otovwe. Patterns of adherence to management among patients with type 2 diabetes mellitus in South-South Region of Nigeria [J]. Journal of Social Health and Diabetes, 2015, 3(2): 115-119
- [25] Beatriz García-Fontana, Sonia Morales-Santana, Victoria Longobardo, et al. Relationship between Proinflammatory and Antioxidant Proteins with the Severity of Cardiovascular Disease in Type 2 Diabetes Mellitus[J]. IJMS, 2015, 16(5): 9469-9483
- [26] Yanwei Li, Lin Li, Christian Hölscher. Incretin-based therapy for type 2 diabetes mellitus is promising for treating neurodegenerative diseases[J]. Reviews in the Neurosciences, 2016, 27(7): 689-711
- [27] M Šeruga, J Makuc, M Završnik, et al. Polymorphism of angiotensin-converting enzyme (rs4340) and diabetic nephropathy in Caucasians with type 2 diabetes mellitus[J]. Balkan Journal of Medical Genetics, 2016, 19(2): 29-34
- [28] S Karachanak-Yankova, R Dimova, D. Nikolova, et al. Epigenetic Alterations in Patients with Type 2 Diabetes Mellitus [J]. Balkan Journal of Medical Genetics, 2015, 18(2): 15-24