Correlation Between Homocysteine and Diabetic Microvascular Complications and Changes Following Pharmacological Intervention: Postprint

Authors: Xie Fang, Lü Dong, Chen Weibin, Lin Yanzu

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Abstract

Objective To investigate the correlation between homocysteine and diabetic microvascular complications and the changes after pharmacological intervention.

Methods Two hundred patients with type 2 diabetes mellitus were divided into a group without microvascular complications and a group with microvascular complications based on the presence of microvascular complications. All patients underwent determination of blood lipids, blood glucose, renal function, and serum homocysteine before treatment and after 6 months of treatment. Additionally, 100 healthy subjects who underwent physical examination during the same period were selected as a normal control group according to the principle of age- and gender-matching.

Results (1) The levels of routinely measured systolic blood pressure (SBP), diastolic blood pressure (DBP), triglycerides (TG), blood lipids including total cholesterol (TC) and low-density lipoprotein (LDL), blood glucose including fasting blood glucose (FBG), 2-hour postprandial blood glucose (2 h PBG), glycated hemoglobin (HbA1), renal function including serum urea nitrogen (SUN) and serum creatinine (Scr), and plasma homocysteine (HCY) in patients from both the group without microvascular complications and the group with microvascular complications were significantly higher than those in the normal control group ($P<0.01$), while HDL levels were significantly lower than those in the normal control group ($P<0.01$); (2) The levels of SBP, DBP, SUN, SCr, and HCY in patients from the group with microvascular complications were significantly higher than those in the group without microvascular complications ($P<0.01$); (3) Multivariate logistic regression analysis revealed that diastolic blood pressure, urea nitrogen, serum creatinine, and homocysteine levels were risk factors for the development of microvascular complications in diabetic patients; (4) After treatment, HCY levels in patients from both the group without

microvascular complications and the group with microvascular complications were significantly decreased compared with those before treatment (P<0.01).

Conclusion Elevated homocysteine level is a high-risk factor for diabetic microvascular complications, and homocysteine levels can be reduced after treatment in patients.

Full Text

Preamble

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Correlation of Homocysteine with Diabetic Microangiopathy and the Change After Drug Intervention

XIE Fang, LÜ Dong, CHEN Weibin, LIN Yanzu
Department of Internal Medicine, Western Hospital of South China Sea, China National Offshore Oil Corporation, Zhanjiang 524057, China

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Abstract

Objective: To explore the correlation of homocysteine with diabetic microangiopathy and the change after drug intervention. **Methods:** A total of 200 patients with type 2 diabetes were selected between January and December 2013. The patients were divided into a group without microvascular disease and a group with microvascular lesion according to the complications. Blood lipid, blood glucose, renal function, and serum homocysteine were detected pretreatment and after 6 months of treatment. A total of 100 healthy subjects with physical examination over the same period were selected as the control group according to the principle of age and gender matching. **Results:** SBP, DBP, TG, TC, LDL, FBG, 2 h PBG, HbA1, SUN, SCr, and HCY in the group without microvascular disease and the group with microvascular lesion were significantly higher than those in the control group (P<0.01), while HDL was significantly lower (P<0.01). SBP, DBP, SUN, SCr, and HCY in the group with microvascular lesion were significantly higher than those in the group without microvascular disease (P<0.01). Multi-factor logistic regression analysis showed that blood pressure, urea nitrogen, serum creatinine, and homocysteine levels are risk factors for microvascular complications in patients with diabetes mellitus. HCY after treatment was significantly lower than that before treatment in both the group without microvascular disease and the group with microvascular lesion (P<0.01). **Conclusion:** High homocysteine levels are a risk factor for diabetic microvascular disease, and the homocysteine levels can be reduced after treatment.

Key words: diabetes; microvascular lesions; homocysteine; clinical correlation

Introduction

Microvascular complications are among the most common and serious chronic complications in patients with type 2 diabetes mellitus. Current evidence suggests that multiple factors participate in the pathogenesis of diabetic microvascular complications, with diabetes duration and degree of glucose metabolism disorder being the most widely recognized. Specifically, the incidence of diabetic microvascular complications increases significantly with diabetes duration, particularly after more than five years, and the risk also rises substantially with higher degrees of glucose metabolism disturbance, especially when chronic hyperglycemia is not effectively controlled. Long-term hyperglycemia leads to non-enzymatic glycation of proteins, and excessive accumulation of glycated proteins causes vascular damage, particularly to systemic microvessels, manifested as vascular wall injury, basement membrane thickening, increased permeability, vascular sclerosis, occlusion, and stenosis, ultimately resulting in diabetic microvascular complications.

Homocysteine levels are closely associated with cardiovascular and cerebrovascular diseases, and elevated homocysteine is an independent risk factor for these conditions. Homocysteine also shows significant correlation with diabetic macrovascular disease. Previous studies have demonstrated that patients with hyperhomocysteinemia have significantly higher carotid intima-media thickness and C-reactive protein levels compared to those with normal homocysteine levels, and carotid intima-media thickness gradually increases with rising homocysteine levels, suggesting that hyperhomocysteinemia is closely related to diabetic cardiovascular and cerebrovascular complications. Additionally, the ankle-brachial index is significantly reduced in hyperhomocysteinemia patients, with correlation analysis showing that the ankle-brachial index decreases significantly as homocysteine levels rise, indicating that homocysteine may participate in the development of diabetic lower extremity vascular disease. Another study revealed that homocysteine and urinary microalbumin levels are higher in diabetic patients with renal microvascular lesions than in those with diabetes alone and in healthy controls, with homocysteine levels increasing with rising blood glucose and worsening renal damage. However, how homocysteine levels change before and after treatment in diabetic microvascular disease patients, and whether these changes correlate with clinical therapeutic efficacy, remains unclear.

Methods

1.1 General Data

A total of 200 patients with newly diagnosed type 2 diabetes mellitus between January 2013 and December 2014 in our hospital were selected and divided into a group without microvascular lesions and a group with microvascular lesions (100 cases each) according to the presence of microvascular complications. Additionally, 100 healthy subjects who underwent physical examination during the same period were selected as the normal control group according to age and gender matching principles.

1.2 Diagnostic, Inclusion, and Exclusion Criteria

1.2.1 Diagnostic Criteria: Type 2 diabetes mellitus was diagnosed according to the 2006 WHO revised diagnostic criteria. Diabetic nephropathy (DN) was diagnosed by microalbuminuria 30 mg/24 h with exclusion of other urinary system diseases. Diabetic retinopathy (DR) was diagnosed according to the 2002 international clinical diabetic retinopathy grading standards.

1.2.2 Inclusion Criteria: Patients in the group without microvascular lesions met the criteria for type 2 diabetes mellitus but not DN or DR. Patients in the group with microvascular lesions met the criteria for type 2 diabetes mellitus and also met the diagnostic criteria for DN and/or DR.

1.2.3 Exclusion Criteria: Patients were excluded if they had: (1) ketoacidosis, non-ketotic hyperosmolar diabetic coma, acute cardiovascular or cerebrovascular disease, or other stress states; (2) concurrent infection; (3) type 1 diabetes, secondary diabetes, gestational diabetes, or other special types of diabetes; (4) concurrent hematological disease; (5) concurrent non-diabetic kidney disease, obstructive nephropathy, urinary stones, infection, or connective tissue disease affecting arteries; (6) concurrent allergic disease; (7) severe heart, liver, or kidney disease; (8) concurrent immune disease receiving hormone therapy; or (9) clinically diagnosed macrovascular disease.

1.3 Laboratory Methods

Healthy subjects underwent physical and laboratory examinations on the day of their health checkup. All diabetic patients underwent physical and laboratory examinations one day before starting treatment, received blood glucose control therapy, and were re-examined after 6 months of treatment. Physical examinations included routine measurements of systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI). Laboratory examinations included fasting peripheral venous blood and 2-hour postprandial venous blood samples for determination of blood lipids, glucose, renal function, and serum homocysteine (the 2-hour postprandial sample was used only for 2-hour postprandial glucose measurement). All measurements were performed using a Beckman BXC600 automatic biochemical analyzer. Blood lipid measurements included

total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL). Blood glucose measurements included fasting blood glucose (FBG), 2-hour postprandial blood glucose (2 h PBG), and glycated hemoglobin (HbA1). Renal function measurements included serum urea nitrogen (SUN) and serum creatinine (Scr).

1.4 Statistical Analysis

SPSS 19.0 statistical software was used. Measurement data were compared among multiple groups using F-test and between two groups using independent samples t-test. Multi-factor logistic regression analysis was used to evaluate the correlation between homocysteine and type 2 diabetic microangiopathy. Paired t-test was used to evaluate changes in serum homocysteine before and after treatment in diabetic patients. $P<0.05$ was considered statistically significant.

Results

2.1 Comparison of Clinical Data

SBP, DBP, TG, TC, LDL, FBG, 2 h PBG, HbA1, SUN, SCr, and HCY levels were significantly higher in both the group without microvascular lesions and the group with microvascular lesions compared to the normal control group ($P<0.01$), while HDL levels were significantly lower ($P<0.01$). The group with microvascular lesions showed significantly higher SBP, DBP, SUN, SCr, and HCY levels compared to the group without microvascular lesions ($P<0.01$). There were no significant differences in gender, age, or BMI among the three groups ($P>0.05$,).

2.2 Logistic Regression Analysis

Using the presence or absence of microvascular lesions as the dependent variable, multi-factor logistic regression analysis was performed with gender, age, BMI, SBP, DBP, TG, TC, HDL, LDL, FBG, 2 h PBG, HbA1, SUN, SCr, and HCY as independent variables. The results showed that DBP, SUN, SCr, and HCY were risk factors for microvascular complications in diabetic patients ().

2.3 Changes in Homocysteine Before and After Treatment

After treatment, HCY levels in both the group without microvascular lesions and the group with microvascular lesions were significantly lower than before treatment ($P<0.01$). Additionally, HCY levels in the group with microvascular lesions remained significantly higher than in the group without microvascular lesions both before and after treatment ($P<0.01$,).

Discussion

Diabetes is the most common disease in clinical endocrinology and a leading cause of disability, death, and increased medical burden. With rapid socioeconomic development, diabetes has become a major public health threat. Currently, there is no cure for diabetes, and the primary treatment goal is to reduce blood glucose levels and minimize diabetic complications. In recent years, with rapid economic growth, lifestyle changes, and population aging, the incidence of diabetes has increased annually. Diabetes, along with cancer and cardiovascular disease, is considered one of the world' s three major diseases, seriously threatening human health and quality of life. Microvascular complications are important complications of diabetes, primarily affecting the retina, kidneys, myocardium, nerve tissue, and toes, with diabetic retinopathy (DR) and diabetic nephropathy (DN) being the main clinical manifestations.

Diabetic nephropathy is one of the leading causes of chronic kidney disease and the primary cause of end-stage renal disease. Early pathological changes in diabetic nephropathy include glomerular hypertrophy, extracellular matrix accumulation, and basement membrane thickening, while advanced stages show diffuse glomerular sclerosis leading to renal failure. The main pathological changes in diabetic retinopathy are alterations in retinal microvascular structure and function, including capillary basement membrane thickening, increased capillary permeability, pericyte loss, and microaneurysm formation, accompanied by decreased retinal blood flow, capillary occlusion, neovascularization, and tractional retinal detachment, ultimately resulting in partial or complete vision loss. Retinal microvascular abnormalities mainly include retinopathy and retinal arteriosclerosis, which are not only a major cause of blindness in adults but have also been shown in recent studies to be closely related to diabetic macrovascular disease. Many clinical diseases are closely related to microcirculation disorders, and diabetic microangiopathy is the pathological basis of diabetic complications and one of the main factors determining diabetes prognosis, seriously affecting clinical outcomes and quality of life.

Homocysteine is a sulfur-containing amino acid and an intermediate product of methionine demethylation metabolism. Under normal conditions, homocysteine is metabolized by the kidneys and maintained at low serum levels. Under certain pathogenic conditions, homocysteine cannot be further converted and is released from retained cells into the blood, causing hyperhomocysteinemia. Hyperhomocysteinemia increases production of oxygen free radicals and hydrogen peroxide, impairs endothelial NO bioactivity leading to endothelial damage, and disrupts the balance between coagulation and fibrinolysis, thereby promoting thrombosis. Studies have shown that hyperhomocysteinemia occurs in diabetes and is associated with vascular complications. Previous research has demonstrated significant correlation between homocysteine and diabetic macrovascular disease. Although numerous studies have examined the relationship between homocysteine and diabetic neuropathy and macrovascular disease, few have investigated the correlation between homocysteine and diabetic microvascular disease.

Our study found that HCY levels were significantly higher in both the group without microvascular lesions and the group with microvascular lesions compared to the normal control group ($P<0.01$), and HCY levels were significantly higher in the group with microvascular lesions than in the group without microvascular lesions ($P<0.01$). Multi-factor logistic regression analysis showed that HCY is a risk factor for microvascular complications in diabetic patients, which may be related to homocysteine-induced vascular endothelial injury and thrombosis promotion. Compared with the study by Qi et al., our results not only showed significantly elevated glycated hemoglobin, homocysteine, and urinary microalbumin levels in type 2 diabetic patients with renal microvascular lesions, but also revealed significantly increased SBP, DBP, SUN, and Scr. Additionally, Yuan et al. reported that Hcy levels were higher in diabetic patients with microvascular lesions than in those with diabetes alone, and that the occurrence of type 2 diabetic microvascular lesions was related to serum Hcy levels, which is consistent with our findings.

Furthermore, our study revealed changes in homocysteine levels before and after treatment in diabetic patients. The results showed that after 6 months of treatment, HCY levels were significantly lower than before treatment in both the group without microvascular lesions and the group with microvascular lesions ($P<0.01$). Therefore, treatment for diabetic microvascular complications can reduce HCY levels and decrease the risk of microvascular complication deterioration.

In conclusion, elevated homocysteine levels are a high-risk factor for diabetic microvascular disease, and treatment can reduce homocysteine levels in patients.

References

[1] 员许民. 血浆血管内皮生长因子与 2 型糖尿病微血管病变的关系研究 [J]. 现代中西医结合杂志, 2011, 20(34): 4327-8.

[2] 王庆国, 丁静, 权翠侠. 同型半胱氨酸在糖尿病视网膜病变诊断中的应用 [J]. 临床荟萃, 2011, 26(2): 108-9.

[3] Zhang D, Chen Y, Xie X, et al. Homocysteine activates vascular smooth muscle cells by DNA demethylation of platelet-derived growth factor in endothelial cells[J]. J Mol Cell Cardiol, 2012, 53(4): 487-96.

[4] Hirsch IB, Brownlee M. Beyond hemoglobin A1c-need for additional markers of risk for diabetic microvascutar complications[J]. JAMA, 2010, 303(22): 22912.

[5] 曹立平, 徐青, 洪丽萍, 等. 原发性高血压患者同型半胱氨酸水平与动脉脉病变及左心室肥厚关系的临床研究 [J]. 中国循环杂志, 2015, 30(2): 133-5.

[6] 刘宋芳, 王述进, 左红, 等. 2 型糖尿病患者同型半胱氨酸与大血管病变的关系 [J]. 中国循环杂志, 2015, 30(2): 130-2.

[7] 亓海萍, 吕卫华, 武琳. 糖化血红蛋白、同型半胱氨酸及尿微量白蛋白与 2 型糖尿病合并肾脏微血管病变的关系研究 [J]. 中国实验诊断学, 2015, 19(11): 1840-3.

[8] Koga T, Fujikawa K, Horai Y, et al. The diagnostic utility of anti-melanoma differentiation-associated gene 5 antibody testing for predicting the prognosis of Japanese patients with DM[J]. Rheumatology, 2012, 51(7): 1278-84.
[9] 李志强, 常红娟, 桑文凤. 特效三消汤加减治疗 2 型糖尿病的临床研究 [J]. 中药材, 2013, 36(1): 163-6.
[10] 中华医学会糖尿病学分会. 中国 2 型糖尿病防治指南 (2010 年版)[M]. 北京: 北京大学医学出版社, 2010: 11-4.
[11] 褶文婷, 黄秋霞. 2 型糖尿病患者血清 25 －羟维生素 D 水平与微血管病变的相关性 [J]. 广东医学, 2015, 36(8): 1229-31.
[12] 张晓会, 赵伟, 郑晓, 等. 中性粒细胞与淋巴细胞比值与 2 型糖尿病微血管病变的相关性研究 [J]. 中华内分泌代谢杂志, 2014, 30(9): 8.
[13] KeeffeJ, Taylor HR, Fotis K, et al. Prevalence and causes of visionloss in Southeast Asia and Oceania: 1990-2010[J]. Br J Ophthalmol, 2014, 98(5): 586-91.
[14] Lim CP, Loo AV, Khaw KW, et al. Plasma, aqueous and vitreous homocysteine levels in proliferative diabetic retinopathy[J]. Br J Ophthalmol, 2012, 96(5): 704-7.
[15] 黎涛. 糖化血红蛋白、同型半胱氨酸、纤维蛋白原与 2 型糖尿病患者微血管病变的相关性 [J]. 海南医学, 2012, 23(24): 91-3.
[16] 李运成. 沙格列汀对糖尿病微血管病变患者血浆 hs-CRP 和 Hcy 水平的影响 [J]. 山东医药, 2014, 54(38): 75-6.
[17] Papatheodorou L, Weiss N. Vascular oxidant stress and inflammation in hyperhomocysteinemia[J]. Antioxid Redox Signal, 2007, 9(11): 1941-58.
[18] Spares AL, Sousa-Mde O, Dusse LM, et al. Type 2 diabetes: assessment of endothelial lesion and fibrinolytic system markers[J]. Blood Coagul Fibrinolysis, 2007, 18(5): 395-9.
[19] Karabag T, Kaya A, Temizhan A, et al. The influence of homocysteine levels on endothelial function and their relation with microvascular complications in T2DM patients without macrovascular disease[J]. Acta Diabetol, 2007, 44(2): 69-75.
[20] Buysschaert M, Dramais AS, Wallemacq PE, et al. Hyperhomocysteinemia in type 2 diabetes: relationship to macroangiopathy, nephropathy, and insulin resistance[J]. FASEB J, 2000, 23(12): 12.
[21] 刘树娇, 唐灵, 陈春莲, 等. 内脂素、同型半胱氨酸、高敏 C 反应蛋白与 2 型糖尿病大血管病变的关系 [J]. 实用医学杂志, 2013, 29(10): 10.
[22] Ozmen B, Ozmen D, Turgan N, et al. The association between homocysteinemia and renal function in patients with type 2 diabetes Mellitus[J]. Ann Clin Lab Sci, 2002, 32(3): 279-86.
[23] 黄漓莉, 苏珂, 于健, 等. 2 型糖尿病患者大血管病变与 Hcy、CysC、hs-CRP 的关系 [J]. 广东医学, 2015, 36(10): 1518-20.
[24] 袁捷, 杜彦丽, 王肃. 2 型糖尿病患者血清 Hcy、CysC、VEGF 水平与微血管病变的关系 [J]. 山东医药, 2015, 55(21): 86-7.

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