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Original Article

Correlation between ankle-brachial pulse wave velocity and urine protein in patients with type 2 diabetes mellitus

Peipei Sun, Xia Wang, Dadong Fei, Qing-Shun Hao, Qiong Luo, Gaofeng Wu, Yuling Liu

Department of Endocrinology, Zaozhuang Municipal Hospital, Zaozhuang, China

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Abstract: Objective: Urine protein has a close relationship with the occurrence and development of diabetic great vascular complications. This work discusses the correlation between the brachial-ankle pulse wave velocity (baPWV) and urine protein in patients with type 2 diabetes mellitus. Methods: 142 patients with type 2 diabetes mellitus were divided into a normal control group [24 h urinary albumin quantity <30 mg, n=84], micro-albuminuria group [30 mg ≤24 h, urinary albumin quantity <300 mg, n=26], and a clinical proteinuria group (24 h urinary albumin quantity ≥300 mg, n=33) according to the level of 24 h urinary albumin. For all patients with type 2 diabetes mellitus, fasting blood-glucose, blood fat, renal function, glycated hemoglobin (GBALC), pancreatic islet function, C-reactive protein and blood pressure were detected, and body mass index was calculated. Then, baPWV was measured by the autopulse method, and the correlation between baPWV and other factors and the multiple regression analysis were conducted using Pearson correlation coefficient analysis. Results: baPWVs of the micro-albuminuria group and the clinical proteinuria group were 1649.19±229.36 cm/s and 1759.21±291.05 cm/s, respectively. Compared with the control group (1522.33±248.37 cm/s), baPWVs in other two groups accelerated significantly (P <0.05). Pearson correlation analysis showed that 24 h urinary albumin was positively related to baPWV (r=0.347, P <0.01). Multiple linear regression showed that baPWV was correlated with 24 h urinary albumin (P <0.05). Conclusion: urine protein of patients with type 2 diabetes mellitus is closely related to baPWV.

Keywords: Type 2 diabetes mellitus, brachial-ankle pulse wave velocity, baPWV, urine protein, atherosclerosis

Introduction

Urine protein is an independent hazard factor in the occurrence and development of diabetic great vascular complications. Moreover, urine protein plays an important role in diabetic atherosclerosis [1]. In recent years, the prediction of atherosclerosis by brachial-ankle pulse wave velocity (baPWV) has been widely applied in clinics [2]. Aiming at providing evidence for an early estimation of angiosclerosis for type 2 diabetes mellitus, the relationship between baPWV of patients with type 2 diabetes mellitus and urine protein was observed in this work.

Data and method

Research object

142 patients with type 2 diabetes mellitus admitted to our department from February 2013 to June 2014 were selected, including 98 male patients and 44 female patients with an average age of 55.44±8.58 years old and average disease course of 7.85±5.62 years. The research objects were divided into 3 groups according to the level of 24 h urinary albumin quantity: normal control group with 24 h urinary albumin quantity <30 mg (n=84), microalbuminuria group with 30 mg ≤24 h urinary albumin quantity <300 mg (n=26), and clinical proteinuria group with 24 h urinary albumin quantity ≥300 mg (n=33). All the research objects met with the standard for type 2 diabetes mellitus regulated by American Diabetes Association in 1997 [3]. In selection, patients with severe cardiac insufficiency, hepatic insufficiency and renal insufficiency, severe malnutrition, stressful situations (such as intense movement and emotional fluctuation), tumor, acute diabetic complications and various acute and

Table 1. Comparison of clinical biochemical data among the three groups (x±s)

Variable	Control group (n=84)	Trace albuminuria group (n=26)	Clinical albuminuria group (n=33)
Gender (male/female)	58/26	19/7	21/11
Smoking history (with/without)	21/63	7/19	10/22
Age (years old)	55.81±8.48	54.15±9.01	55.55±8.67
Duration (years)	7.32±5.37	8.89±7.27	8.36±4.66
BMI (kg/m^2)	25.58±3.17	25.73±3.47	25.81±3.59
Systolic blood pressure (mmHg)	133.60±18.90	140.37±15.18	151.21±13.69**
Diastolic blood pressure (mmHg)	78.04±11.59	81.67±10.00	89.09±10.86**
Three acyl glycerin (mmol/L)	1.61±1.08	1.89±1.18	1.93±1.08
Total cholesterol (mmol/L)	4.46±0.86	4.46±0.89	4.84±1.17
Fasting plasma glucose (mmol/L)	7.54±2.57	7.78±3.00	8.72±3.30
high density lipoprotein (mmol/L)	1.05±0.23	1.00±0.30	1.04±0.26
Low density lipoprotein (mmol/L)	2.73±0.65	2.61±0.92	2.99±0.89
Glycated hemoglobin (%)	8.80±1.90	8.60±1.67	9.15±2.01
Creatinine (μmol/L)	57.10±15.15	61.44±20.76	88.70±30.54**,#
Blood urea nitrogen (mmol/L)	5.42±1.28	6.08±1.92	6.67±2.23**,#
Uric acid (μmol/L)	276.56±74.45	290.89±63.40	358.91±82.78**,#
CRP (mg/L)	3.75±2.46	4.94±2.99*	5.29±2.89**
Fasting c-peptide (ng/mL)	1.25±0.77	1.66±1.13	1.57±0.79
Postprandial 2 hc peptide (ng/mL)	3.26±1.87	3.44±2.18	3.32±1.61
baPWV (cm/s)	1522.33±248.37	1649.19±229.36*	1759.21±291.0**

Compared with the control group, *P <0.05, **P <0.01; Compared with the trace albuminuria group, #P <0.05.

chronic wasting diseases were all excluded. This work was approved by the Ethic Committee of our hospital, and all the research objects signed Informed Consent.

Research method

Research objects being limosis for 12 h lay on their backs in the morning for routine sampling of 10 ml venous blood and anti-coagulanted with heparin. Blood fat, renal function and blood glucose (by the glucose oxidase method), C-creative protein (by CRP, immunity transmission turbidity), glycated hemoglobin (GBALC) (by high performance liquid chromatography), 24 h urinary albumin (by immunoturbidimetry twice, and the mean was taken) and pancreatic islet function (by radiommunoassay) were measured using a HITACHI 7600 fully automatic biochemical analyzer (Japan). After the patient laid on their back for 5~10 min, an Omron BP203 RPE II arteriosclerosis detector made in Japan was used to measure baPWV at room temperature. The cuffs were placed on both upper arms and a Doppler probe was placed on the brachial artery of the elbow to obtain signals and measure the systolic pressure on both brachial arteries. The same cuff was placed on the ankle and the Doppler probe on the arteria tibialis posterior and arteria dorsalis pedis to obtain a signal and measure the systolic pressure in both ankle arteries. The values of baPWV on all four limbs were measured and averaged. All the patients were interviewed and provided the following indices: sex, age, body mass index (BMI), blood pressure and duration of diabetes.

Statistical analysis

SPSS 17.0 statistical software was used for data analysis. The measurement data were presented as mean ± standard deviation (SD). Single factor analysis of variance was conducted for the comparison among various groups, and an LSD test was conducted for the pair wise comparison. Pearson correlation analysis was used in the correlation analysis, and partial correlation analysis of corrected age and blood pressure was conducted. A multiple linear regression model was conducted for the influence factor analysis on baPWV. If $P \leq 0.05$, there is a statistical significance.

Table 2. Multiple stepwise regression analysis of the relative factors for baPWV

Variable	β	SE	t value	*P* value	β 95% CI
Constant	174.930	173.573	1.008	0.315	-168.277~518.138
Systolic blood pressure	8.297	0.948	8.756	0.000	6.424~10.171
Age	8.943	1.979	4.520	0.000	5.031~12.856
24 h Urinary albumin	0.270	0.120	2.246	0.026	0.032~0.508
Three acyl glycerin	39.034	14.916	2.617	0.010	9.541~68.527
BMI	-12.280	4.771	-2.574	0.011	-21.714~-2.847

Results

Comparison of general data

Compared with the control group, no differences with any statistical significance (P >0.05) in age, sex, disease course, BMI, blood pressure, etc were found in the microalbuminuria group. Compared with the control group, the clinical proteinuria group had higher blood pressure with a statistically significant difference (P < 0.05), but there were no statistically significant differences in age, sex, disease course, BMI, etc. The difference between the clinical proteinuria group and the microalbuminuria group had no statistical significance (P >0.05) in age, sex, disease course, BMI, etc. See **Table 1**.

Comparison between baPWV and laboratory index

Compared with the control group, the microalbuminuria group had higher CRP and accelerated baPWV with statistically significant difference (P <0.05). However, the difference of blood fat, renal function, fasting blood-glucose, glycated hemoglobin, pancreatic islet function, etc. between the two groups had no statistical significance (P >0.05). Compared with the control group, the clinical proteinuria group had higher CRP, creatinine, blood urea nitrogen and uric acid, and accelerated baPWV with statistically significant difference (P <0.01). Compared with the microalbuminuria group, the clinical proteinuria group had higher levels of creatinine and uric acid with statistically significant difference (P <0.05), but the difference of baPWV and blood, fasting blood-glucose and other laboratory indices had no statistical significance (P >0.05). See in **Table 1**.

Pearson correlation and multiple linear regression analysis

Pearson correlation analysis showed that baPWV was positively related to age (r=0.436, P <0.01), disease course (r=0.252, P <0.01), sex (r=0.328, P <0.01), systolic pressure (r= 0.693, P <0.01), diastolic blood pressure (r= 0.587, P <0.01), creatinine (r=0.294, P <0.01), blood urea nitrogen (r=0.334, P <0.01), uric acid (r=0.170, P <0.01) and 24 h urinary albumin (r=0.347, P <0.01). Partial correlation analysis showed that baPWV and 24 h urinary albumin still had significant correlation after correcting age, disease course, sex and blood pressure (r=0.191, P <0.05). Multiple linear regression analysis was conducted with baPWV as a dependent variable and age, BMI, CRP, systolic pressure, diastolic blood pressure, 24 h urinary albumin, blood fat; creatinine, glycated hemoglobin and pancreatic islet function as independent variables. The results showed that systolic pressure, diastolic blood pressure, 24 h urinary albumin, triglyceride and BMI were the independent factors affecting baPWV, in which the systolic pressure had the biggest influence on baPWV. See in **Table 2**.

Discussions

Diabetic great vascular complications are the primary reasons for the disability and death of diabetics, while the atherosclerosis is the basis of its occurrence and development. Atherosclerosis includes fatty degeneration (atheroma) and vessel hardening (sclerosis) [4-6]. As a recognized index for arterial stiffness [7, 8], baPWV reflects the change in vascular wall function. Moreover, baPWV is also an important index to predict vessel disease of atherosclerosis for patients with high blood pressure and end-stage renal failure [9-11]. As a simple and operable measurement method, baPWV has been widely applied in clinics [12].

This work found that among patients with type 2 diabetes mellitus, the severity of proteinuria was closely related to the speed of baPWV. This

means that once the patient has a lesion in the renal capillaries, the arterial compliance of the great vessel may also be reduced. Therefore, the vessel's ossification will be more severe, while the risk of cardiovascular disease may be significantly increased. However, this work cannot explain whether there is causality between proteinuria and baPWV, and this requires to be verified with further research. There are only a few researches on the specific mechanism of correlations between the proteinuria increase and baPWV acceleration and angiosclerosis as yet. Some references have reported that the increase of proteinuria may be related to the advanced glycosylated end products and extracellular matrix [13]. Advanced glycosylated end products play an important role in diabetic complications. The advanced glycosylated end products accelerated in patients with diabetic renal diseases may combine with specific receptors expressed on sertoli cells to cause lesions of the sertoli cells and generate proteinuria [14, 15]. Moreover, the acceleration of advanced glycosylated end products in the great vessel may also cause diabetic great vascular complications. These showed that the two complications have a common pathophysoilogical way. Rigalleau et al. [16] thought that the great vessel lesion of patients with type 2 diabetes mellitus was closely related to renal lesions, while the advanced glycosylated end products play a role in bridging both lesions. In addition, vessel functions are affected by extracellular matrix, which is the composition of the vessel wall [17]. At present, some researchers have proved that the extracellular matrix of the skeletal muscle capillary may change with proteinuria level [18]. This indirectly proved that the proteinuria may affect the function of the vessel.

In addition, it had been found in this work that the CRP of the micro-albuminuria group was higher than that of the control group. The acceleration of baPWV showed that the inflammatory level of patients with type 2 diabetes mellitus combined with proteinuria was higher. Some researchers have proved that CRP was not only the independent risk factor of atherosclerosis, but also the independent risk factor of great vessel lesions of type 2 diabetes mellitus [19, 20]. Therefore, it is speculated that the inflammatory reaction in vessels of patients in the micro-albuminuria group is relatively strong. This strong reaction causes the occurrence of vessel atherosclerosis and the acceleration of baPWV. Therefore, the relationship between proteinuria and atherosclerosis may be related to the inflammatory reaction in the vessel. For the clinical proteinuria group, CRP, baPWV, creatinine, blood urea nitrogen and uric acid are all higher than that of the control group. It can be believed that patients in the clinical proteinuria group have more protein in their urine, so urinary protein is the risk factor for progressive development of chronic renal insufficiency. Therefore, the index of renal function is higher than that in the control group. Renal insufficiency is closely related to great vessel lesion [21-23]. We speculated that this may be one of the reasons for obvious baPWV acceleration. Similarly, Pearson correlation analysis and partial correlation analysis in this work showed that baPWV had significant correlation with 24 h urinary albumin. Multi-factor regression analysis showed that systolic pressure has the largest influence on baPWV. Hypertensive patients may have afferent glomerular arteriole plump and degeneration, sclerosis and shrinkage, and increased urinary albumin excretion [24]. Therefore, for patients with type 2 diabetes mellitus combined with proteinuria, the blood pressure should be controlled within normal limits to avoid the deterioration of glomerulus injury.

In conclusion, the significant increase of baPWV in patients with type 2 diabetes mellitus combined with proteinuria is closely related to atherosclerosis and renal lesion of type 2 diabetes mellitus. Therefore, the blood glucose and pressure of diabetics should be controlled in clinics, and inflammatory level and urine protein should be reduced to avoid the occurrence of diabetic great vascular complications. This work is only an observational experiment research on the correlation between the severity of proteinuria of patients with type 2 diabetes mellitus and the speed of baPWV. However, this work cannot explain the causality and specific mechanism, so this work has a certain limitation. In the future, further research is required to discuss the specific mechanism.

Disclosure of conflict of interest

None.

Address correspondence to: Qing-Shun Hao, Department of Endocrinology, Zaozhuang Municipal Hospital, No. 41 of Longtou Road, Zaozhuang 277102, Shandong Province, China. Tel: +86 13863290786; Fax: +86 0632 3288018; E-mail: qingshunhaodoc@163.com

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