Decrease Heart Rate Variability But Preserve Postural Blood Pressure Change in Type 2 Diabetes with Microalbuminuria

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Background: This study compares the cardiovascular autonomic function in type 2 diabetes with and without microalbuminuria, in order to identify the possible links between early nephropathy and diabetic autonomic neuropathy (DAN).

Methods: Cardiovascular reflex tests were performed to determine the cardiovascular autonomic function. Thirty cases of type 2 diabetes with microalbuminuria were studied for evidence of DAN to compare with a normoalbuminuric group of 56 diabetic patients.

Results: There was an increased prevalence of autonomic dysfunction in patients with microalbuminuria (63.3% in the microalbuminuria group *vs.* 40.0% in the normoalbuminuric controls, $p = 0.001$). These patients had lower heart rate variability during single breathing tests (6.9 ± 4.3 *vs.* 9.6 ± 3.6 beats/minute, $p = 0.005$), during 6 consecutive breathings (5.8 ± 3.6 *vs.* 8.2 ± 3.3 beats/minute, $p = 0.005$), after standing up (12.2 ± 4.6 *vs.* 15.0 ± 5.2 beats/minute, $p = 0.012$), and during the Valsalva maneuver (11.3 ± 3.5 *vs.* 13.2 ± 3.6 beats/minute, $p = 0.022$). The heart rate variability with these stresses was revealed to be less favorable in subjects with microalbuminuria. However, blood pressure (BP) changes from the sitting to standing position were not significantly different for systolic BP (11.5 ± 10.7 *vs.* 10.7 ± 7.8 mmHg, $p = 0.741$) and diastolic BP (5.2 ± 4.4 *vs.* 5.9 ± 4.0 mmHg, $p = 0.451$) between the 2 groups.

Conclusion: Type 2 diabetic patients with microalbuminuria have diminished heart rate variability in response to deep breathing, change of position and the Valsalva maneuver, but they preserve BP response to postural change. Therefore, microalbuminuria seems to be associated with early DAN, but not with advanced DAN. [*J Chin Med Assoc* 2006;69(6):254–258]

Key Words: cardiovascular reflex tests, diabetic autonomic neuropathy, glycated hemoglobin (A1C), microalbuminuria, type 2 diabetes

Introduction

Early detection and identification of the risks for the development of diabetic complications are important to minimize the human suffering and costs incurred.[1] Microalbuminuria is an early sign of diabetic nephropathy that predicts progression to renal disease.[2,3] When diabetes is associated with microalbuminuria, the relative risk of developing cardiovascular diseases increases 3- to 8-fold.[4,5] Diabetic autonomic

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neuropathy (DAN) affects the parasympathetic and sympathetic nerves, producing a functional change in the innervated territories.[6] DAN interferes with the cardiovascular system with a sequence of decreasing heart rate variability with stress, followed by resting tachycardia and then orthostatic hypotension.[7] Cardiovascular reflex (CVR) tests based on heart rate variability and blood pressure (BP) changes with stress are the most commonly used methods to detect DAN.[8,9] Both increased urinary albumin excretion and cardiovascular autonomic neuropathy are strong predictors of mortality in patients with type 2 diabetes.[10,11] Thus, there are several possible links between diabetic nephropathy and cardiovascular autonomic neuropathy. In the present study, CVR tests were performed in type 2 diabetes cases with or without microalbuminuria. We tried to find the link between early nephropathy and DAN, especially at the early stage of DAN.

Methods

Subjects

At Taipei Veterans General Hospital, a tertiary-level medical center, patients with type 2 diabetes are screened on a regular basis for evidence of early complications. One hundred patients signed informed consents and completed screening for complications during the period from August to November 2001. The assessment included tests for early nephropathy (albumin-to-creatinine ratio in early morning urine samples), autonomic neuropathy (CVR tests), and other diabetic profiles. The protocol was approved by the hospital's institutional review board.

Detection of albuminuria

We used a single-voiding sample of urine prepared in the early morning and calculated the ratio of urine albumin-to-creatinine (UACR) excretion in order to test a large number of outpatients.[12] Urinary albumin concentration was measured by rate nephelometry (IMMAGE® Immunochemistry System; Beckman Coulter Inc, Fullerton, CA, USA). The interassay coefficient of variance (CV) was 7.5% at 0.56 mg/dL and 2.0% at 3.19 mg/dL (n = 80). Urinary creatinine was measured using a Hitachi 7600 automatic analyzer (Hitachi Ltd, Tokyo, Japan). The interassay CV for this assay was < 2.0% at 2.0 mg/dL (n = 10).

Cardiovascular reflex tests

The CVR tests, which included heart rate variability with stress and orthostatic BP changes, were performed as previously described.[11] The CVR tests were monitored on a 7D polygraph with a 7P4F tachograph, a PTTL photoelectric transducer, an EKG 7P4 preamplifier (all from Grass Instruments Inc, Quincy, MA, USA) and other appropriate accessories. Instant heart rate, individual pulses and EKG (Lead II) were recorded simultaneously on each subject. Subjects with a history of cardiac arrhythmia or those taking medication such as α-blocker, β-blocker, diuretics, or other drugs known to influence autonomic nerve function, were excluded.

Heart rate response to a single deep breathing: Subjects sat quietly and then breathed deeply. Results were expressed as the difference of the heart rate (maximum minus minimum) throughout the procedure.

Heart rate response to 6 consecutive breathings: Subjects sat quietly and then took 6 consecutive breathings at a rate of 6 breaths/minute. Results were expressed as the mean difference of the heart rate over the last 3 breathing cycles.

Heart rate response to standing up: Subjects lay quietly on a couch and then stood up unaided. Results were expressed as the difference between maximum and minimum heart rates after standing up from a lying position.

Heart rate response to Valsalva maneuver: Subjects sat quietly and then blew into a mouthpiece connected to a sphingomanometer at a pressure of 40 mmHg for 30 seconds. Results were expressed as the different heart rates during the maneuver.

Blood pressure response to standing up: BP was measured using a standard cuff sphygmomanometer while subjects sat and then stood up. The differences in BP were taken as the measure of postural BP change.

The normal range of heart rate variability was obtained from the lower 95% confidence intervals in healthy Chinese adults aged 16–75 years.[13,14] An abnormal CVR test was defined as scoring ≥ 3 following the diagnostic criteria shown in Table 1.

Other measurements

Baseline BP was measured using a mercury sphygmomanometer (Kogyo Co, Tokyo, Japan) twice in the sitting position after 10 minutes of rest. The mean of the measurements was used. Glycemic control was documented in terms of glycated hemoglobin (A1C) at the time of testing. A1C was measured using high-performance liquid chromatography (HPLC) instruments (HLC-723 GHB IIIs, Tosoh, Japan). Each subject also had a fasting blood sample for measurement of cholesterol and triglyceride.

Table 1. Diagnostic criteria and abnormal number of cardiovascular reflex tests

	Diagnostic criteria	Score
Heart rate variability		
Single deep breath	HRV < 8 beats/min*	1
6 consecutive breaths	HRV < 7 beats/min*	2
Lying to standing	HRV < 17 beats/min	1
Valsalva maneuver	HRV < 13 beats/min	1
Blood pressure change		
Sitting to standing	SBP fall > 25 mmHg or DBP fall > 10 mmHg	1

**Diagnostic criteria also adjusted by age. HRV = heart rate variability; SBP = systolic blood pressure; DBP = diastolic blood pressure.*

Statistical analysis

Statistical analysis was performed using SPSS version 12.0 (SPSS Inc, Chicago, IL, USA) for Windows. Results were expressed as frequency and mean ± standard deviation. The χ^2 test and the independent Student *t* test were used to assess the association of the categorical and quantitative variables with the outcome variables. Statistical significance was defined as $p < 0.05$.

Results

Based on the UACR, subjects fell into 3 groups: 56 subjects with normoalbuminuria (UACR < 30 mg/gCr), 30 subjects with microalbuminuria (UACR between 30 and 300 mg/gCr), and 14 subjects with macroalbuminuria (UACR > 300 mg/gCr). The demographic and clinical data of subjects with normoalbuminuria and microalbuminuria are shown in Table 2. Subjects with macroalbuminuria were eventually excluded from this study. Type 2 diabetic patients with microalbuminuria had higher A1C levels (8.3 ± 2.0 *vs.* 7.4 ± 1.7%, $p = 0.037$) and systolic BP (144.9 ± 24.8 *vs.* 132.3 ± 17.2 mmHg, $p = 0.023$).

There was an increased prevalence of autonomic dysfunction in patients with microalbuminuria (63.3% in the microalbuminuric group *vs.* 40.0% in normoalbuminuric controls, $p = 0.001$). The detailed results of the CVR tests are shown in Table 3. Patients with microalbuminuria had lower heart rate variability during single breathing tests (6.9 ± 4.3 *vs.* 9.6 ± 3.6 beats/minute, $p = 0.005$), during 6 consecutive breathings (5.8 ± 3.6 *vs.* 8.2 ± 3.3 beats/minute, $p = 0.005$), after standing up (12.2 ± 4.6 *vs.* 15.0 ± 5.2 beats/minute, $p = 0.012$), and during the Valsalva maneuver (11.3 ± 3.5 *vs.* 13.2 ± 3.6 beats/minute, $p = 0.022$). Heart rate variability during these stress tests was revealed to be less favorable in subjects with microalbuminuria. However, BP changes from the sitting to standing position were not significantly different for systolic BP (11.5 ± 10.7 *vs.* 10.7 ± 7.8 mmHg, $p = 0.741$) and diastolic BP (5.2 ± 4.4 *vs.* 5.9 ± 4.0 mmHg, $p = 0.451$) between the 2 groups.

Table 2. Clinical and biochemical features in type 2 diabetic patients with normoalbuminuria and microalbuminuria

	Patients with microalbuminuria	Patients with normoalbuminuria	*p*
Case number	30	56	
Gender (male/female)	15/15	36/20	0.203
Age (yr)	65.7 ± 7.8	63.6 ± 10.7	0.283
Diabetes duration (yr)	11.2 ± 6.1	10.1 ± 6.7	0.433
A1C	8.32 ± 2.05	7.38 ± 1.68	0.037
BMI (kg/m^2)	25.59 ± 2.96	24.62 ± 3.00	0.190
Systolic BP (mmHg)	144.9 ± 24.8	132.3 ± 17.2	0.023
Diastolic BP (mmHg)	72.7 ± 11.5	73.9 ± 9.5	0.661
Cholesterol (mg/dL)	203.8 ± 39.1	193.2 ± 39.2	0.289
Triglyceride (mg/dL)	213.5 ± 110.1	162.3 ± 134.3	0.099

A1C = glycated hemoglobin; BMI = body mass index; BP = blood pressure.

Table 3. Cardiovascular reflex tests in patients with normoalbuminuria and microalbuminuria

	Patients with microalbuminuria (n = 30)	Patients with normoalbuminuria (n = 56)	p
HRV in single deep breath	6.9 ± 4.3	9.6 ± 3.6	0.005
HRV in 6 consecutive breaths	5.8 ± 3.6	8.2 ± 3.3	0.005
HRV in lying to standing	12.2 ± 4.6	15.0 ± 5.2	0.012
HRV in Valsalva maneuver	11.3 ± 3.5	13.2 ± 3.6	0.022
SBP change	11.5 ± 10.7	10.7 ± 7.8	0.667*
DBP change	5.2 ± 4.4	5.9 ± 4.0	0.451

**ANCOVA test for SBP result is significant difference in the baseline value. HRV = heart rate variability; SBP = systolic blood pressure; DBP = diastolic blood pressure.*

Discussion

Our study demonstrated that impaired heart rate variability responses to stress are more frequent in the microalbuminuria group, but postural BP changes are not different between the 2 groups. The CVR study is important because its frequency is an indicator of the probable existence of other autonomic dysfunctions (digestive, reproductive, urinary, and others),[9,15] as well as an increased risk of mortality.[11,16] We performed 5 measurements of CVR tests: 4 of them reflected mainly the parasympathetic function (heart rate variability in response to stresses) and 1 reflected mainly the sympathetic function (postural BP changes). Ewing et al[7] described that the earliest abnormalities of DAN is a decrease in heart rate variability during deep breathing, followed by alterations in heart rate upon standing and then the Valsalva maneuver; postural hypotension is a late event. This sequence suggests that parasympathetic efferents are damaged first, followed by the sympathetic outflow. In the present study, type 2 diabetic patients with microalbuminuria had diminished heart rate variability responses to stress, but preserved BP responses to postural change. Microalbuminuria is an early stage of diabetic nephropathy, which is also a risk marker for the development of overt nephropathy.[2,3] These findings further support the hypothesis that diminished heart rate variability in response to stress may also be an early stage of DAN, and play a role in the development of advanced DAN or other diabetic autonomic neuropathies.

Microalbuminuria has been emphasized as a risk factor of not only diabetic nephropathy,[2,3] but also coronary artery disease.[4,5] It is also an independent risk factor of mortality.[10] In the present study, microalbuminuria was found in 30% of type 2 diabetic patients, with a mean diabetic duration of 11.2 years. Similar results have been reported in large epidemiologic studies.[17,18] The potential limitation of using a single-voiding sample to calculate the ratio of albumin-to-creatinine excretion is the variability in urinary albumin excretion. However, we could use this method in order to test a large number of outpatients.

A clinical association between DAN and nephropathy in diabetes has been documented in some studies.[19–21] Hyperglycemia may be a common factor in the pathogenesis of these complications, and poor glycemic control has been demonstrated to influence the development and progression of both nephropathy and neuropathy. The association between DAN and nephropathy might have a pathogenetic significance rather than being due to the simple coexistence of the 2 diabetic complications. In this study, the association was strong, but the mechanisms underlying this striking relationship remain unclear. Further investigation could provide useful insights into the complex and multifactorial pathogenesis of diabetic complications.

The findings in this study, therefore, have potential clinical implications. In the UK Prospective Diabetes Study, the development and progression of both microalbuminuria and neuropathy was decreased by intensive therapy, including glycemic[22] and BP control.[23] Furthermore, microalbuminuria in diabetic patients can be reversed by meticulous control of diabetes, but it should be irreversible in patients with overt nephropathy.[24] Recently, Burger et al suggested that a reversible metabolic component of DAN exists in patients with early DAN, but not in advanced DAN.[25] Thus, there are some links between early DAN and microalbuminuria, and patients with either complication should be targeted for more intensive therapy.

In conclusion, our study demonstrated that type 2 diabetic patients with microalbuminuria had diminished heart rate variability in response to some stresses, but BP response to postural change was preserved.

In other words, the microalbuminuric patients increased the prevalence rate of early DAN, but not that of advanced DAN. These findings, therefore, suggest that type 2 diabetic patients with either microalbuminuria or early DAN should be targeted for more intensive therapy.

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