

Relationship Between Cardiovascular Autonomic (Dys)Function and Microalbuminuria in Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic autonomic neuropathy is a serious and common complication of diabetes mellitus and in fact it is one of the most overlooked complications, thus very limited clinical and research data are available on early renal and cardiovascular autonomic complications in type 2 diabetes mellitus.

Aims & Objective: To determine the possible association of elevated albumin excretion rate with cardiovascular autonomic activity in type 2 diabetes mellitus.

Materials and methods: A cross-sectional study was conducted with one hundred and fifteen patients of type 2 diabetes mellitus. Microalbuminuria was defined as Albumin Excretion Rate (AER) > 30 mg/24 hr in an early morning urine sample. Nine parameters reflecting different aspects of cardiovascular autonomic function were measured and were summarized in a single cardiovascular autonomic function score (CAFS). The association between cardiovascular autonomic dysfunction and microalbuminuria was estimated by multiple linear regressions.

Results: Patients with microalbuminuria had low levels of the autonomic function parameters i.e. mean CAFS, indicating impaired autonomic function. This association was consistent with increasing AER, and remained significant after multivariate adjustment for other clinical factors predictive of microalbuminuria. In additional analysis, we examined the autonomic function tests combined on the part of autonomic nervous system they predominantly represent. The results of these alternative combinations were comparable to those of the CAFS score.

Conclusion: Cardiovascular autonomic dysfunction was independently associated with microalbuminuria in patients with type 2 diabetes mellitus, and that this association is independent of other previously identified determinants of albuminuria in type 2 diabetes mellitus. Therefore cardiovascular autonomic function tests should be monitored to pay attention to major potential cardiovascular complications even in asymptomatic patients, but especially among those with microalbuminuria.

KEY WORDS: Microalbuminuria; Cardiovascular Autonomic Function Tests; Type 2 Diabetes Mellitus

INTRODUCTION

There are currently 40.5 million patients of diabetes mellitus in India and this number is expected to increase to about 60.9 million by the year 2025.^[1] This increase is a warning sign for clinicians to be vigilant not only for adequate diabetes mellitus management, but also for early indicators of microvascular and macrovascular complications. Nephropathy and cardiovascular dysautonomia are devastating microvascular complications of diabetes mellitus that tend to occur concurrently in adults who experience the ravages of diabetes mellitus.² The clinical manifestations of cardiovascular autonomic neuropathy include orthostatic hypotension, abnormalities in heart rate control, and decreased heart rate variability (HRV).^[2] Microalbuminuria is recognized as the earliest marker of renal disease and is also strongly associated with increased risk of cardiovascular complications, including atherosclerotic coronary artery disease, stroke, peripheral vascular disease, and cardiovascular mortality.^[3] This association is independent of other known cardiovascular risk factors such as hypertension, dyslipidemia, obesity, smoking, and impaired renal function.³ Several mechanisms, notably endothelial dysfunction and low-grade inflammation, have been proposed to explain, at least in part, the increased risk of cardiovascular mortality in individuals with microalbuminuria.^[4] Cardiovascular autonomic dysfunction (CAD) could potentially constitute another such mechanism. Indeed, few studies have previously shown that CAD is associated with microalbuminuria, especially in individuals with impaired glucose metabolism and diabetes mellitus.^[5-6] In addition, CAD is associated with cardiovascular mortality and can potentially link microalbuminuria to cardiovascular mortality by arrhythmogenic or atherogenic effects.^[7] Despite the degree of interest shown in the subject, there is still limited information on the relationship between microalbuminuria and cardiovascular autonomic function, especially in type 2 diabetes mellitus. Thus, in the present study, we investigated the pattern of autonomic activity in this population with and without

microalbuminuria and made an attempt to evaluate if there is an independent relation between increased urinary albumin excretion and subclinical autonomic neuropathy.

MATERIALS AND METHODS

This was a prospective observational study conducted from February 2010 to September 2011. The study protocol was approved by the Human Research Ethical Committee and informed consent was obtained from all the patients before enrolling into the study. The study group consisted of 115 type 2 diabetes mellitus patients with either sex of varying age. The history of diabetes mellitus was based on patient self report of a prior physician diagnosis and was under treatment with oral anti-diabetic agents and/or insulin. Patients with overt albuminuria, congestive cardiac failure, pre-existing macrovascular condition, urinary tract infection, any severe illness (such as malignancy, severe infection, respiratory disease, liver disease), impairment of speech, hearing, vision, or cognition, history of neurological disease, using ACE inhibitors and/or drugs known to influence autonomic nerve function (namely antiparkinsonism drugs, phenytoin, or parasympatholytic, parasympathomimetic, and sympathomimetic drugs), pregnant females or who had given birth within the preceding six weeks, inability to stand independently, inability to complete cardiovascular autonomic tests, lack of approval by physician and patients showing disinterest were excluded from the study.

All patients were studied as outpatient. Patients were interviewed for medical and nutritional history. Present and past history of each case was recorded in detail regarding their general information i.e. name, age, sex, address, religion, occupation, economic status, nutritional and personal habits, education, medication and history suggestive of any systemic illness. Each patient was then examined for various anthropometric parameters: Weight (Kg) and height (meters) were measured (using Omron digital body weight scale HN-286 and SECA 206 wall mounted metal tapes respectively). Body

Mass Index (BMI) was calculated by Weight (Kg) / height squared (m^2).^[8] Waist circumference was assessed in the standing position, midway between the highest point of the iliac crest and the lowest point of the costal margin in the mid-axillary line. Hip circumference was measured at the level of the femoral greater trochanter. All anthropometric measures reflect the average of 3 measurements (measured by same person on same instrument to avoid inter-instrument and inter personal variation). Blood pressure (BP) was measured three times in the seated position after 10 minutes of rest with a standard manual mercury sphygmomanometer (Diamond Deluxe Industrial Electronics and Products). The recorded pressure of the three measurements was averaged. Patients were assigned to a category of hypertensive status according to the Seventh Report of the Joint National Committee, JNC 7.^[9] Hypertension (HTN) stage 2 was defined with a systolic blood pressure equal to or exceeding 160 mmHg or diastolic BP equal to or exceeding 100 mmHg, and those who had used BP lowering medications. Normal blood pressure was considered to be a systolic reading < 140 mmHg and a diastolic reading < 90 mmHg. Readings between these levels were classified as stage 1 hypertension. Age was defined as the age at the time of interview (though no documentary proof had been entertained) and the date of diagnosis of diabetes mellitus was obtained from the patient.

All 115 patients were asked to collect a first morning mid stream urine sample for analysis of albumin excretion. Urine collection was carried out during unrestricted daily life activity. The urinary albumin concentration was determined by Micral test using commercially available assay kits from Roche Diagnostics (Mannheim, Germany). The micral test is a test-strip method in which the color reaction is mediated by an antibody-bound enzyme.^[10] The mean inter- and intra-assay coefficients of variation were 3.6 and 4.4%, respectively. Normoalbuminuria was defined as Albumin Excretion Rate (AER) < 30 mg/24 hr, and Microalbuminuria as AER 30- 300 mg/24 hr. Microalbuminuria was graded as mild (20-50 mg/24 hr), moderate (50-100 mg/24 hr),

or severe (100-300 mg/24 hr) depending on the color change in the strip. Results were confirmed after 2 measurements done in a space of 6 months. If the results of a 2nd measurement placed the patient in a different category from that based on the first measurement, a 3rd urine sample was obtained to confirm either the first or second measurement.

A sample of blood was drawn after overnight fasting of 12 hours with an aseptic technique. Serum and plasma was separated from the blood sample and were subjected for following analytical procedures: Plasma glucose was measured using the glucose oxidase method. HbA1c was measured with a DSS machine using the ion exchange chromatography method. Serum cholesterol by Cholesterol Oxidase p-aminophenazone (CHOD-PAP), serum triglycerides by Glycerol phosphate oxidase p-aminophenazone (GPOPAP) methods and high-density lipoprotein (HDL) cholesterol by precipitation method. Low-density lipoprotein (LDL) cholesterol was calculated with Friedewald's formula. Adult Treatment Panel III (ATPIII) criteria^[11] were used to classify plasma lipid levels. Biochemical tests were analyzed on a Bayer express plus auto analyzer. Quality was controlled using standard solutions.

Cardiovascular autonomic function tests (CAFT) which includes tests for heart rate variability and responses to the certain maneuver^[12-14], were conducted by one investigator. Patients were asked to fast for 2 hours before CAFT and to avoid taking caffeine, antihistamines or other over-the counter cold medications for a period of 48 hours before the tests. An electrocardiographic registration was obtained from bipolar chest leads, R-R intervals were obtained by using a QRS detector with an accuracy of 1 ms. Beat-to beat systolic and diastolic blood pressure levels were measured noninvasively on the right middle finger with the Finapres method (Type BP2300; Ohmeda, Englewood).^[15] Cardiac cycle duration (R-R interval) and continuous finger arterial pressure were continuously recorded on a computer-based data-acquisition system. When off-line

spectral analysis showed that breathing was not performed at the appropriate frequency, the record was discarded. The test session started with a resting period of at least 10 min.

Tests were performed under three conditions {and the following measures of cardiovascular autonomic function were used}:

1. During spontaneous breathing over 3 min in the supine position {proportion of the total RR intervals that have differences of successive R-R intervals greater than 50 milliseconds [pNN50], SD of all normal to normal R-R intervals, i.e. sinus rhythm, RR interval [SDNN (ms)], low-frequency [LF (ms²)] power, in absolute units i.e. energy in the power spectrum between 0.04 and 0.12 Hz, high frequency [HF (ms²)] power in absolute units i.e. energy in the power spectrum between 0.12 and 0.40 Hz, and LF/(LF+HF) i.e. the ratio of LF-power to the sum of LF- and HF-power}
2. During six deep breaths over 1 min in the supine position {expiration to inspiration heart rate [EI_{HR} difference (beat/min)] difference: the difference between intrabreath maximum and minimum HR averaged over six consecutive breaths. It was determined during a 1-min period in which the participant was instructed to breath at a rate of six breaths per minute (5s in, 5s out).
3. During an active change from lying to standing {SBP difference (mmHg) i.e. the systolic blood pressure after standing up (mean between 1.5 and 2.0 min after standing) minus the supine systolic blood pressure (mean of 30 s), R-R interval maximum [RR_{max}] i.e. maximum R-R interval between 15 and 30 seconds after standing up divided by minimum R-R interval within 15 seconds after standing up, and R-R interval maximum divided by minimum [RR_{max/min}] i.e. maximum R-R interval between 15 and 30 seconds after standing up divided by minimum R-R interval within 15 seconds after standing up}

The EI difference, RR_{max} and HF power predominantly reflect parasympathetic function,

the SBP difference mainly reflect sympathetic function while pNN50, SDNN, LF power, LF/(LF+HF), and RR_{max/min} reflects both (parasympathetic and sympathetic) functions.^[13,16] However, the specificity of these tests for the two different types of autonomic function is limited.^[17] Results were discarded if multiple nonsinus beats occurred during testing, if standing up took >10 s, or if the recordings were technically unsuccessful.

Statistical Methods:

All analyses were performed using SPSS statistical software (SPSS, version 15.0). Routine bivariate tests were used to test for group differences between patients with and without microalbuminuria. Two-group comparisons were made using X² or Fisher's exact tests (when any expected cell frequency was <5) for categorical variables and Student's *t* tests or one-way ANOVA for continuous variables. The nonparametric Kruskal-Wallis test was used for highly skewed continuous variables. Correlations between the nine autonomic function measures were calculated using Pearson's correlation coefficients, if required after log-transformation. Based on the nine measures of cardiovascular autonomic function, a summary cardiovascular autonomic (dys)function score (CAFS) was constructed as follows. First, the results of each measurement were divided into quartiles. A patient was assigned 0 points if the result was in the most normal quartile, 1 point if the result was in the second quartile, 2 points if the result was in the third quartile and 3 points if the result was in the most abnormal quartile. When all nine measures were completed successfully, then the scores of each were added together. The result is a CAFS ranging from 0 (good) to 27 (poor). Multiple logistical regression analysis was used to identify the association between microalbuminuria and cardiovascular autonomic (dys)function. For all analyses, two-sided probability values < 0.05 were considered statistically.

RESULTS

Of the one hundred fifteen patients included, thirty one had microalbuminuria. The general characteristics of study group are shown in Table 1.

Table-1: General Characteristics of Study Groups

Characteristic /Variable	Normoalbuminuric patients (n=84)	Microalbuminuric patients (n=31)	p value
Age (years)	46.8 ± 9.7	53.2 ± 8.8	< 0.05
Duration of DM (years)	6.3 ± 4.1	8.4 ± 6.1	< 0.05
BMI (kg/m ²)	25.4 ± 3.7	29.6 ± 4.1	< 0.05
Waist-to-hip ratio	0.88 ± 0.06	0.95 ± 0.08	< 0.05
Systolic BP (mmHg)	136.2 ± 18.5	142.8 ± 19.6	< 0.05
Diastolic BP (mmHg)	78.0 ± 8.4	84.4 ± 10.8	< 0.05
HTN (%)	48.0	67.7	< 0.05
Total cholesterol (mg/dl)	198.7 ± 43.6	204.5 ± 46.9	0.36
Triglycerides (mg/dl)	138.2 ± 40.4	186.7 ± 41.1	< 0.05
HDL-cholesterol (mg/dl)	46.8 ± 6.2	44.9 ± 5.4	0.21
LDL-cholesterol (mg/dl)	119.4 ± 32.5	126.5 ± 31.9	0.84

Values are expressed as mean + standard deviation

Age, BMI, waist-hip ratio, triglycerides, blood pressure and HbA1c were significantly related to the presence of microalbuminuria in bivariate analysis. Concerning cardiovascular autonomic function tests, patients who had

microalbuminuria had significantly lower score on all parameters, than those who were normoalbuminuric: RR_{max} (208 ± 82 Vs 243 ± 91ms; p< 0.05), RR_{max/min} (1.09 ± 0.09 Vs 1.22 ± 0.13ms; p< 0.05), SBP difference (- 9.8 ± 13.1 Vs - 5.8 ± 14.3mmHg; p< 0.05), SDNN (63 ± 22 Vs 112 ± 24ms; p< 0.05), pNN50 (11 ± 4 Vs 22 ± 8; p< 0.05), LF power (162 Vs 233ms²; p< 0.05), HF power (129 Vs 174ms²; p< 0.05), LF/(LF+HF)(0.47 ± 0.13 Vs 0.57 ± 0.13; p< 0.05), EI_{HRdifference} (8.5 Vs 12.7 beats/min; p< 0.05) (Table 2).

Table-2: Cardiovascular Autonomic Function Tests in Study Group

Characteristic /Variable	Normoalbuminuric patients (n=84)	Microalbuminuric patients (n=31)	p value
RR _{max} (ms)	243 ± 91	208 ± 82	< 0.05
RR _{max/min} (ms)	1.22 ± 0.13	1.09 ± 0.09	< 0.05
SBP difference (mmHg)	- 5.8 ± 14.3	- 9.8 ± 13.1	< 0.05
SDNN (ms)	112 ± 24	63 ± 22	< 0.05
pNN 50	22 ± 8	11 ± 4	< 0.05
LF power (ms ²)	233 (65-923)	162 (21-632)	< 0.05
HF power (ms ²)	174 (45-798)	129 (25-605)	< 0.05
LF/(LF+HF)	0.57 ± 0.13	0.47 ± 0.13	< 0.05
EI _{HRdifference} (beats/min)	12.7 (2.1-43.6)	8.5 (2.8-24.2)	< 0.05
Total CAFS* score	14.4	22.7	< 0.05

Values are expressed as mean + standard deviation; % and median (range); CAFS: cardiovascular autonomic (dys)function score

Table-3: Association Between Microalbuminuria and Cardiovascular Autonomic Function Tests

	Crude Model			Model A†			Model B‡		
	β*	95% CI	p	β*	95% CI	p	β*	95% CI	P
CAFS§	0.44	0.22-0.69	<0.05	0.29	0.09-0.42	<0.05	0.26	-0.08-0.39	<0.05
CAFT (parasympathetic)	0.41	0.19-0.66	<0.05	0.34	0.11-0.46	<0.05	0.21	-0.06-0.38	<0.05
CAFT(Sympathetic)	0.21	-0.09-0.36	<0.05	0.20	-0.06-0.32	<0.05	0.18	-0.04-0.33	<0.05
CAFT(parasympathetic & Sympathetic)	0.35	0.16-0.59	<0.05	0.26	0.08-0.41	<0.05	0.24	0.05-0.33	<0.05

β*: Difference in CAFS score (Microalbuminuric patients Vs Normoalbuminuric patients); Crude model: Univariate analysis; Model A†: Adjusted for sex and age; Model B‡: Model A plus adjustments for hypertension, Waist-hip ratio, BMI, Total cholesterol, triglycerides, LDL-C and HDL-C; CAFS§: cardiovascular autonomic (dys)function score

Table 3 displays the association of CAFS in patients with microalbuminuria, total CAFS was independently related to the presence of microalbuminuria in the study group ($\beta=0.44$ [95% CI 0.22-0.69]) (Table 3, crude model). These associations were attenuated after adjustments for age and sex ($\beta=0.29$ [95% CI 0.09-0.42]) (Table 3, Model A). Further adjustment for other potential confounding factors only slightly further attenuated the result ($\beta=0.26$ [95% CI -0.08-0.39]). Comparable results were obtained when tests were combined on the part of the autonomic nervous system they predominantly represent. Logistic regression analyses revealed that impaired autonomic function was consistently associated with microalbuminuria. Compared with the patients whose albumin excretion rate (AER) was $<30\text{mg/day}$, autonomic dysfunction was progressively significantly associated with elevated AER (Table 4).

Table-4: Multiple Logistical Regression Analyses

	Crude Model	Model A*	Model B
Normoalbuminuria	1.00	1.00	1.00
Severe microalbuminuria (100–300 mg/24 hr)	1.98 (0.81-3.33)	1.41 (0.72-3.01)	1.36 (0.66-2.91)
Moderate microalbuminuria (50–100 mg/24 hr)	1.76 (0.85-3.45)	1.35 (0.66-3.12)	1.31 (0.61-2.82)
Mild microalbuminuria (20–50 mg/24 hr)	1.61 (0.77-2.97)	1.26 (0.67-2.12)	1.22 (0.64-2.06)

Model A*: Adjusted for sex and age; Model B†: Model A plus adjustments for hypertension, Waist-hip ratio, BMI, Total cholesterol, triglycerides, LDL-C and HDL-C

DISCUSSION

This was a cross-sectional observational study designed to investigate the pattern of cardiovascular autonomic activity in type 2 diabetic patients with and without microalbuminuria. In the present study we have demonstrated subclinical autonomic neuropathy (estimated from the mean of nine standardized tests) is related to the presence of microalbuminuria in an age and sex-stratified random sample of type 2 diabetic population, further it was observed that with an increased

AER the neural dysfunction becomes more abundant and severe. Moreover, this relationship between an increased AER and subclinical autonomic neuropathy was independently significant by logistic regression analysis including several demographic, clinical and metabolic variables.

Previous research has explored the relationships between cardiovascular autonomic neuropathy, variables derived from 24-h blood pressure recordings, and microalbuminuria.^[18] Some studies have examined autonomic cardiovascular function in relation to albuminuria in diabetes mellitus. An early study found higher urinary albumin excretion rates in patients with impaired HR variability, which is a feature of cardiovascular autonomic failure.^[19] Another report indicated that autonomic cardiovascular dysfunction measured with only a single test (deep breathing) was related to macroalbuminuria in a large ($n = 949$) sample of relatively young and strictly hypertensive patients.^[20] Finally, a study found that albuminuria was related to Valsalva and breathing ratios only in patients with a duration of type 2 diabetes mellitus of >1 year²¹. However, in all these studies the association of autonomic dysfunction with (micro)albuminuria is consistent. These findings are in line with those reported herein. Compared with these previous studies, our study has the advantage, in a way that, we characterized patient's cardiovascular autonomic dysfunction as comprehensively as possible by conducting nine autonomic function tests, which are thought to reflect all aspects of cardiovascular autonomic function, and this study has also shown that these associations were especially strong in a high-risk population, defined by the presence of diabetes mellitus, having high AER. The subgroup analyses should, however, be interpreted with some caution because they apply to a much smaller number of patients.

Two explanations exist for a possible causal relationship between cardiovascular autonomic function and urinary albumin excretion. First, a reduced nightly drop in blood pressure, which is

a feature of autonomic dysfunction, may result in albuminuria.^[22] Second, a disturbance in glomerular arteriolar autoregulation may result in an inability of the glomerular apparatus to counteract hyperglycemia-associated glomerular hypertension and hyperfiltration.^[23] Another possibility is that the association we found is not causal but simply reflects an association between two diabetic complications caused by largely the same set of risk factors.

In the present study, we also examined the autonomic function tests combined on the part of the autonomic nervous system they predominantly represent (Table 3). The results of these alternative combinations of autonomic function tests were comparable to those of the CAFS total score, but we acknowledge that these analyses may not have been specific enough, as most authors agree that a clear distinction between parasympathetic or sympathetic dysfunction cannot be made on the basis of these tests.

We did find, however, that cardiovascular autonomic dysfunction was associated with microalbuminuria independent of blood pressure level, suggesting that cardiovascular autonomic impairment may be involved in the pathogenesis of diabetic renal disease through mechanisms independent of blood pressure. The renal vasculature is extensively innervated by the sympathetic nervous system. Our findings are consistent with the hypothesis suggested by others that impairment of autonomic function leads to increased renal blood flow^[24], glomerular hyperfiltration, and sodium excretion, all of which accelerate progression to diabetic microalbuminuria.^[25] Alternatively, the metabolic and vascular changes associated with diabetes mellitus may adversely affect both renal and cardiovascular autonomic function through other mechanisms.

Nonetheless, this study has few limitations. Firstly, sampling may not be representative to all patients and/or the general population. Secondly, the design was cross-sectional and therefore does not provide predictive data. Thirdly, the

proxy definition of diabetes mellitus was used in the study and auto antibodies screening such as Anti-GAD analyses was not assessed for patients. Fourth, effect of antihypertensive drugs were not taken into account, and fact is that a significant number of patients were receiving beta blockers, and it is well known that beta blockers affect autonomic nervous system function.^[16] Fifth, the spectral analyses were performed during 3 minute. Measurement of HRV during a longer period may be more reliable, although measurements obtained in time periods as short as 2 minute correlate highly with 24-hour measurements^[26], and final possible concern is whether combining several autonomic function measures in a single score is legitimate. We constructed the CAFS with the purpose of enhancing power because a battery of autonomic function measures, by definition show a higher reproducibility than any single measurement^[27] and, the results herein reported with the CAFS total score were more powerful than results obtained on the basis of each individual test (separately), because these results would be more strongly affected by misclassification (likely to be random), causing an underestimation of the strength of the associations. Also, the nine measures are thought to convey distinct information about cardiovascular autonomic function, although the specificity for the specific subtype of autonomic function (sympathetic vs. parasympathetic) should not be overestimated.^[17]

CONCLUSION

Our study shows that autonomic cardiovascular dysfunction is associated with the occurrence of microalbuminuria, in patients with type 2 diabetes mellitus, and this association is independent of age, sex, blood pressure, and other previously identified determinants of microalbuminuria in type 2 diabetics. These data are consistent with the hypothesis that increased urinary albumin excretion rate and neuropathy, have a common pathogenesis. However, further studies are needed to elucidate the details of involved mechanisms. Thus overall, findings of this study have implications for the care of

diabetic patients. Patients and care providers should give priority for careful assessment of subtle cardiovascular changes (marker of autonomic dysfunction), along with micralbuminuria, in need of referral and treatment to avert future complications. So, this study suggests that there is a strong need for earlier and regular evaluation of autonomic nervous system in type 2 diabetes mellitus to prevent further complications.

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