

# The Comparison of QT Dispersion and 24 Hour Ambulatory Blood Pressure Monitoring Amongst Diabetic Patients With and Without Microalbuminuria

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## Summary

Diabetes mellitus is an important coronary artery disease risk factor. The presence of microalbuminuria, which indicates renal involvement in diabetic patients, is associated with an increased cardiovascular risk. There are suggestions that diabetic patients with microalbuminuria have more adverse risk profile such as higher ambulatory blood pressure and total cholesterol levels to account for the increased cardiovascular morbidity and mortality. QT dispersion is increasingly being recognized as a prognostic factor for coronary artery disease and sudden death. Some studies have suggested that QT dispersion is an important predictor of mortality in Type II diabetic patients. Our cross sectional study was to compare the QT dispersion and 24 hour ambulatory blood pressure monitoring between diabetic patients with microalbuminuria and those without microalbuminuria. Diabetic patients with overt coronary artery disease were excluded from the study. A total of 108 patients were recruited of which 57 patients had microalbuminuria and 51 were without microalbuminuria. The mean value of QT dispersion was significantly higher in patients with microalbuminuria than in patients without microalbuminuria ( $58.9 \pm 27.9$  ms vs.  $47.1 \pm 25.0$  ms,  $p < 0.05$ ). The mean 24 hour systolic and diastolic blood pressures were significantly higher in patients with microalbuminuria than in patients without microalbuminuria ( $129.5 \pm 12.3$  mm Hg vs  $122.3 \pm 10.2$  mm Hg,  $p < 0.05$  and  $78.4 \pm 6.9$  mm Hg vs  $75.3 \pm 6.8$  mm Hg,  $p < 0.05$ , respectively). Our study suggests that QT dispersion prolongation, related perhaps to some autonomic dysfunction, is an early manifestation of cardiovascular aberration in diabetic patients with microalbuminuria. The higher blood pressure levels recorded during a 24-hour period in diabetics with microalbuminuria could also possibly account for the worse cardiovascular outcome in this group of patients.

**Key Words:** QT dispersion, 24-hour ambulatory blood pressure, Diabetes mellitus, Microalbuminuria

## Introduction

Both insulin dependent and non-insulin dependent diabetes mellitus are recognized risk factors of coronary artery disease. Atherosclerosis occurs earlier in diabetic

patients compared to the general population<sup>1</sup>. The presence of microalbuminuria, an early clinical sign of diabetic nephropathy, is associated with increased cardiovascular risk and early cardiovascular mortality in

This article was accepted: 4 August 2003

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type 2 diabetic patients<sup>24</sup>. The apparent association of microalbuminuria with coronary artery disease could be related to the presence of adverse risk profile in these patients. Patients with microalbuminuria were found to have higher blood pressure and total cholesterol levels as compared to those without microalbuminuria.

QT dispersion and heart rate adjusted QT length [corrected QT interval (QTC)] are increasingly being recognized as prognostic factors for coronary artery disease (CAD) and sudden death. QT dispersion, which is a measure of inter-lead QT variability, may reflect the underlying disturbances of ventricular recovery<sup>5</sup>. QT dispersion has been shown to be able to predict cardiac death in patients with chronic heart failure, peripheral vascular disease and essential hypertension<sup>6,7</sup>. Naas et al found that QT dispersion and QTC dispersion are excellent predictors of cardiac death in patients with non-insulin dependent diabetes mellitus<sup>8</sup>. Sawicki et al also concluded that QT interval dispersion is an important predictor of mortality in non-insulin dependent diabetic patients<sup>9</sup>.

Diabetic patients had been reported to have higher mean systolic and diastolic blood pressures recorded over a 24-hour period<sup>10</sup>. The presence of microalbuminuria that reflects renal involvement in diabetic patients has been reported as a major determinant of ambulatory blood pressure<sup>11,12</sup>.

We undertook this study to determine whether diabetic patients with microalbuminuria but without the presence of overt coronary artery disease had more prolonged QT dispersion or higher 24-hour blood pressure level than those without microalbuminuria. Our research hypothesis was that asymptomatic diabetic patients with microalbuminuria had cardiac involvement that might be subclinical as reflected by more prolonged QT dispersion and higher 24-hour blood pressure levels as compared to those without microalbuminuria.

## Materials and Methods

Our cross-sectional study recruited diabetic patients who were attending the diabetes and endocrinology clinic in Hospital UKM from July 1998 to January 1999. Male and female diabetic patients (IDDM and NIDDM) aged between 16 and 80 years old were included in the study. The criteria for the diagnosis of diabetes mellitus was fasting venous glucose level of more than 6.7

mmol/L or random venous glucose level of more than 10.0 mmol/L. The exclusion criteria included patients with hypertension (systolic and diastolic blood pressures of more than 140 and 90 mm Hg respectively), the presence of clinical (as determined by the Rose questionnaire) and electrocardiographic evidence of ischaemic heart disease, renal impairment (serum creatinine above 133 mmol/L), treatment with antiarrhythmic drugs and non-sinus rhythm ECGs. Patients with ECG showing bundle branch block were also excluded from the study.

Patients who fulfilled the criteria had a 12 lead ECG recording for the measurement of QT dispersion and a 24-hour blood pressure monitoring. All 12 standard ECG leads were recorded by means of a six-channel ECG recorder at a paper speed of 25 mm/s. For analysis of QT dispersion, QT intervals were measured manually in as many of the 12 leads as possible. The QT intervals were measured from the onset of the QRS to the end of the T wave, which was defined as return to the T-P baseline. When U wave was present, the QT was measured to the nadir of the curve between the T and U waves. Wherever possible, two consecutive cycles were measured in each of the 12 ECG leads and from the two values a mean QT value was calculated. When the end of the T waves could not be reliably identified, that lead was not included in the subsequent analysis. Only ECGs with at least eight analyzable leads were included in the analysis. QT dispersion was defined as the difference between maximum QT and minimum QT intervals occurring in any of the 12 leads in which they could be reliably measured. The same investigator analyzed twenty ECG tracings on two different occasions for assessment of intraobserver variability. For the evaluation of interobserver variability, a second investigator who was blinded to the results obtained by the first investigator analyzed twenty ECG tracings. 24-hour blood pressure recording was performed with Spacelabs Inc ambulatory blood pressure device model 90207-30. Mean systolic and diastolic blood pressure levels over 24-hour period with mean daytime and nighttime arterial pressures were analyzed respectively.

Quantitative measurement of albumin in the urine was carried out by an enzyme-linked immunosorbent assay using kits (Exocell Inc., Philadelphia). The intra-assay coefficient of variations (CV) at 6.1 and 51.0 µg/ml were 6.4 and 7.4% respectively, with the corresponding inter-assay CVs were 14.2 and 12.8% respectively. Urine creatinine was determined colorimetrically using

reagents supplied by Roche Products Ltd UK. Microalbuminuria was defined as albumin: creatinine ratio of 2.5-25 mg/mmol for male and 3.5-25 mg/mmol for female, and/or albumin excretion rate of 20-200 µg/min or 30-300 mg/24 hour. HbA1c was measured by HPLC using Variant Analyzer, Bio-Rad Laboratories where normal reference was 4-6%.

#### Statistical Analysis

Values of QT dispersion and blood pressure levels were expressed as mean  $\pm$  standard deviation (SD). As the data displayed Gaussian distribution, comparison between means was performed using the Student's t-test. A p value of less than 0.05 was considered statistically significant. All statistical analyses were performed with the SPSS Statistical Software (version 10, SPSS Inc.).

#### Results

A total of 108 consecutive diabetic patients (46 males, 62 females) who fulfilled the inclusion criteria were recruited in the study. The patients' age ranged from 17 years to 77 years old with a mean of 45.7 years. A total of 18 patients (16.7%) were insulin dependent diabetes mellitus (IDDM) patients while 90 patients (83.3%) were non-insulin dependent diabetes mellitus patients (NIDDM). The glycosylated hemoglobin (HbA1c) level of the patients ranged from a minimum of 4.9% to a maximum of 15.1% with a mean level of 8.8%.

There were 57 patients (52.8%) with microalbuminuria compared to 51 patients (47.2%) without

microalbuminuria. There was no significant difference in the mean age of patients with microalbuminuria compared to those without microalbuminuria ( $46.9 \pm 12.8$  years vs  $44.4 \pm 13.3$  years,  $p = \text{NS}$ ). There was also no significant difference in the mean HbA1c level between patients with microalbuminuria and those without microalbuminuria ( $8.8 \pm 2.4\%$ ,  $p = \text{NS}$ ). Comparisons between patients with microalbuminuria are shown in Table I.

The mean value of QT dispersion was significantly higher in patients with microalbuminuria compared to those without microalbuminuria ( $58.9 \pm 27.9$  ms vs.  $47.1 \pm 25.0$  ms,  $p < 0.05$ ) (Table II). There was no significant difference between the number of leads measured between these two groups of patients ( $10.8 \pm 1.2$  vs.  $11.1 \pm 1.0$ ,  $p$  is not significant).

Comparisons of the mean systolic pressure, the mean diastolic pressure, the mean arterial pressure, the mean daytime (0600 hour to 1800 hour) arterial pressure and the mean night time (1800 hour to 0600 hour) arterial pressure between patients with and without microalbuminuria are shown in Table III. The mean systolic and diastolic pressures were significantly higher in the group of patients with microalbuminuria compared to those without microalbuminuria ( $129.5 \pm 12.3$  mm Hg vs.  $122.3 \pm 10.2$  mm Hg,  $p < 0.05$  and  $78.4 \pm 6.9$  mm Hg vs.  $75.3 \pm 6.8$  mm Hg,  $p < 0.05$ , respectively). The mean daytime and nighttime arterial pressures were also significantly raised in patients with microalbuminuria compared to those without microalbuminuria ( $97.1 \pm 7.8$  mm Hg vs.  $92.7 \pm 6.8$  mm Hg,  $p < 0.05$ , and  $94.9 \pm 7.9$  mm Hg vs.  $89.4 \pm 7.3$  mm Hg,  $p < 0.05$ , respectively).

**Table I: Baseline characteristics of patients with microalbuminuria and those without microalbuminuria.**

	Microalbuminuria (n = 57)	Non Microalbuminuria (n = 51)	p-value
Mean age (years)	$46.9 \pm 12.8$	$44.4 \pm 13.3$	NS
Male	22	22	NS
Female	33	29	NS
IDDM	6	12	NS
NIDDM	51	39	NS
Mean HbA1c (%)	$8.8 \pm 2.1$	$8.6 \pm 2.4$	NS

NS indicates not significant

**Table II: QT dispersion and number of leads measured in patients with and without microalbuminuria**

	Microalbuminuria	Non microalbuminuria	p-value
QTd (msec)	58.9 ± 27.9	47.1 ± 25.0	0.03
Number of leads measured	10.8 ± 1.2	11.1 ± 1.0	NS

NS indicates not significant

**Table III: Comparison of ambulatory blood pressure monitoring parameters between patients with and without microalbuminuria**

Parameters	Microalbuminuria	Non microalbuminuria	p-value
Mean systolic pressure (mm Hg)	129.5 ± 12.3	122.3 ± 10.2	0.003
Mean diastolic pressure (mm Hg)	78.4 ± 6.9	75.3 ± 6.8	0.033
Mean arterial pressure (mm Hg)	95.9 ± 7.4	91.7 ± 7.3	0.007
Mean daytime (0600 to 1800 hr) arterial pressure (mm Hg)	97.1 ± 7.8	92.7 ± 6.8	0.005
Mean nighttime (1800 to 0600 hr) arterial pressure (mm Hg)	98.9 ± 7.9	89.4 ± 7.3	0.001

## Discussion

Our study showed that QT dispersion was significantly higher in diabetic patients with microalbuminuria compared to those without microalbuminuria. The increased QT dispersion reflects the underlying abnormality in the recovery of ventricular excitability<sup>5,13</sup>. Langen et al<sup>14</sup> had reported that diabetic patients with cardiovascular autonomic neuropathy had significantly increased QTc interval and QT dispersion compared to those without evidence of cardiovascular autonomic neuropathy. As the presence of autonomic neuropathy is not known in our patients, the increased QT dispersion in patients with microalbuminuria would suggest that some degree of imbalance in cardiac sympathetic innervation might be present in these patients. This might further suggest that the presence of microalbuminuria, in diabetic patients without overt coronary artery disease, could be an early indicator of cardiovascular autonomic neuropathy. Naas et al<sup>6</sup> had shown in their cohort study that QT and QTc dispersion were accurate predictors of cardiac death in newly diagnosed non-insulin dependent diabetics. They further suggested that QT interval could therefore be used as a screening test to select diabetic patients for more extensive cardiac investigations. The presence of microalbuminuria in diabetic patients could therefore be an additional indicator that more extensive cardiac assessment would probably be required. We found no significant difference in the HbA1c level between the patients with and without microalbuminuria in this study. Therefore, glycaemic control could not account

for the difference in the QT dispersion in this study. The Zutphen Elderly study<sup>15</sup> had shown that the QTc was significantly associated with fasting glucose, insulin, and C-peptide and glucose levels 60 and 120 min after an oral glucose load.

Our study had demonstrated significantly higher mean systolic and mean diastolic pressures in diabetic patients with microalbuminuria compared to those without microalbuminuria. The mean daytime and nighttime arterial pressures were also significantly higher in diabetics with microalbuminuria. This was an interesting finding as none of the diabetic patients were hypertensive by the World Health Organization (WHO) criteria. The presence of microalbuminuria in normotensive diabetic patients could therefore be an early marker of the development of overt hypertension in the future. The presence of microalbuminuria, which reflects renal involvement in diabetic patients, had been reported as a major determinant of ambulatory blood pressure<sup>11,12</sup>. Sochett et al<sup>16</sup> also reported in their study that microalbuminuric IDDM patients differed from the normoalbuminuric subjects in having higher mean 24 hour and overnight systolic pressure. This was further supported by the study of Hansen et al<sup>17</sup> which had shown that in IDDM patients, ambulatory blood pressure was influenced by urinary albumin excretion even in the normal range

This study suggests that there is early cardiac involvement in diabetic patients with microalbuminuria but not in those without microalbuminuria. This

abnormal cardiac involvement includes probable cardiac autonomic dysfunction that manifests as QT dispersion prolongation. Although there is no overt clinical evidence of heart disease in our patients, this early cardiac dysfunction is detected by the simple method of recording a 12-lead ECG and measuring the QT dispersion. In addition, higher ambulatory blood pressure was also recorded in these normotensive diabetic patients with microalbuminuria. The presence of microalbuminuria in normotensive diabetic patients

without clinical signs and symptoms of coronary artery disease could therefore perhaps be the trigger to alert us of possible adverse cardiovascular profile in these patients.

### Acknowledgements

This study was supported by a research grant provided by the Faculty of Medicine, UKM (F/32/98).

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