Association of microalbuminuria with left ventricular dysfunction in Nigerian normotensive type 2 diabetes patients

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Abstract

Background: Diabetes mellitus (DM) is a risk factor for left ventricular (LV) dysfunction, and microalbuminuria is frequently associated with DM. This study aimed to compare LV function among normotensive type 2 diabetes (T2DM) patients with normoalbuminuria, those with microalbuminuria, and healthy controls.

Methods: This was a cross-sectional study conducted at the diabetes and cardiology clinics of the University of Uyo Teaching Hospital, Uyo, Akwa-Ibom State, Nigeria, from January 2013 to March 2014. Microalbuminuria was tested for using Micral test strips, and echocardiography-derived indices of LV function were compared among the three groups.

Results: Sixty-three normoalbuminuric, 71 microalbuminuric T2DM patients and 59 healthy controls were recruited. Mean age of participants was 50 ± 8 years and the three groups were age and gender matched (p = 0.23, p = 0.36, respectively). LV diastolic dysfunction (LVDD) showed a stepwise increase from the healthy controls to the normoalbuminuric to the microalbuminuric T2DM patients (16.9 vs 61.9 vs 78.9%, respectively) (p < 0.001), while E/A ratio and fractional shortening showed a significant stepwise decrease (both p < 0.001). LV systolic dysfunction was rare among the three groups. Microalbuminuria showed a strong direct association with LVDD (OR 3.58, 95% CI: 1.99–6.82, p < 0.001). Age remained independently associated with LVDD (OR 1.10, 95% CI: 1.03–1.17, p = 0.003).

Conclusions: LV diastolic function was altered in Nigerian normotensive T2DM patients, and the presence of microalbuminuria with DM had additional effects on this abnormality. Early screening for DM and microalbuminuria could identify individuals with high cardiovascular risk and possibly abnormal LV function.

Keywords: diabetes mellitus, microalbuminuria, left ventricle, diastolic dysfunction

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Diabetes mellitus (DM) is associated with diverse cardiovascular conditions such as myocardial infarction, heart failure (HF), stroke and diabetic cardiomyopathy (DMCMP), which are the leading causes of diabetes-related morbidity and mortality.1,2 Previous studies elsewhere3,4 and in Nigeria5 have demonstrated left ventricular diastolic dysfunction (LVDD) in normotensive diabetics, supporting the existence of DMCMP.

The Framingham Heart Study showed that the frequency of HF is twice as high in diabetic men and five times higher in diabetic women compared with age-matched controls, and that this increased incidence of HF persisted despite correction for age, hypertension, obesity, hypercholesterolaemia and coronary artery disease (CAD).6 An increased risk for developing HF in prospective analyses after correction for confounding variables has also been reported.7 Therefore screening for the presence of DMCMP at the earliest stage is appropriate for the early detection and prevention of HF.

The most sensitive non-invasive test for detection of LV dysfunction is a two-dimensional echocardiogram with pulsed-wave Doppler.8 As the cost of echocardiography is high, a less expensive pre-screening test for monitoring further deterioration in cardiac function in normotensive type 2 diabetes (T2DM) patients is needed. Microalbuminuria (MCA), a known marker of glomerular endothelial dysfunction, is also associated with microangiopathy in T2DM patients.9 It is suggested here that detection of MCA may also serve as an inexpensive pre-screening test for monitoring further deterioration in cardiac function in normotensive T2DM Nigerian patients. This study was designed
to determine whether the presence of MCA in T2DM Nigerian subjects could demonstrate further deterioration in cardiac function in these patients.

Methods
The study was done in accordance with the Declaration of Helsinki and the protocol was approved by the University of Uyo Teaching Hospital, Uyo Institutional Ethical Research Committee (IHREC) reference number UUTH/AD/S/96/VOL.XII/38. The study was conducted in the diabetes and cardiology clinics of UUTH between January 2013 and March 2014. Two hundred participants were recruited; 134 consecutive diabetic patients, diagnosed according to the American Diabetes Association, or who were on oral antidiabetic drugs, and 59 non-diabetic age- and gender-matched controls completed the study.

Exclusion criteria were hypertension (blood pressure ≥ 140/90 mmHg or use of antihypertensive drugs), age above 65 years, macroalbuminuria, serum creatinine of ≥ 1.5 mg/dl, chest deformity or long-standing chest disease evidenced on chest X-ray, sickle cell disease, urinary tract infection, pregnancy, cardiac conditions such as arrhythmia, heart failure, valvular heart disease, pericardial disease, congenital heart disease, and ischaemic heart disease as evidenced by clinical, electrocardiographic and echocardiographic features.

Age, gender and duration of diabetes were recorded for each subject. Weight was determined in kilograms (kg) using a weighing scale, height using a stadiometer, and waist and hip circumferences (WC and HC) were measured in centimeters (cm) using a tape measure. Body mass index (BMI), body surface area (BSA) and waist:hip ratio (WHR) were calculated.

Blood pressure was measured using an Accosson mercury sphygmomanometer with appropriate sized cuff at the brachial artery. Korotkoff phase 1 was used for systolic (SBP) and phase 5 for diastolic blood pressure (DBP) after at least 15 minutes of rest in a sitting position. Pulse rate (PR) was measured at the radial artery. The mean of three consecutive measurements, taken at five-minute intervals, was recorded. An overnight fasting venous blood sample was collected for measurement of levels of plasma glucose, creatinine and urea, and lipid profile using standard protocols.

A two-step microalbuminuria screening process was conducted. Combur 10 test strip (Roche Diagnostics, Mannheim, Germany), a visual colorimetric semi-quantitative urine test strip, was used to test for protein, blood, nitrite and leucocyte levels. If all were absent then detection of microalbuminuria was performed on the same urine sample.

Microalbuminuria was determined using Micral test strips, an optically read semi-quantitative immunosassay method (Roche Diagnostics, Australia) with a sensitivity and specificity of 80 and 88%, respectively. There are four colour blocks on the test strip corresponding to negative (or 0), 20, 50 and 100 mg/l of albumin. The test was done on two occasions; the first was random urine samples (RUS) and the second was first morning void (FMV) urine samples of the subjects.

Microalbuminuria was considered to be present when the two urine samples produced a reaction colour corresponding to 20 mg/l or more. The result from the FMV urine sample was recorded as the MCA status of the subject. It has been suggested that MCA detected in the FMV urine sample corresponds better with 24-hour urinary albumin excretion (UAE) than microalbuminuria measured in a RUS, because it is less influenced by physical exercise and diet.

Echocardiographic examination was performed with the patient in the left lateral decubitus position using a Hewlett-Packard Sonos 4500 echocardiography machine with a 3.5-MHz transducer. Measurements were taken under two-dimensional guided M-mode, as recommended by the American Society of Echocardiography (ASE).

Endocardial fractional shortening (FS) was calculated automatically by the echocardiography machine using the formula:

$$FS = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

where LVIDd is left ventricular internal dimension in diastole and LVIDs is left ventricular internal dimension in systole.

Left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV) were calculated automatically by the echocardiography machine from M-mode-derived LV dimensions, using Teicholz’s formula:

$$LVEDV \text{ or } LVESV = \frac{7.0 \times LVID^3}{2.4 + LVID}$$

Ejection fraction (EF) was calculated using the formula:

$$EF = \frac{EDV - ESV}{EDV} \times 100\%$$

The LV systolic function was considered normal if the EF was greater than 50% and/or FS was greater than 25%. The LV diastolic function was assessed using Doppler modalities. Early (E) and atrial (A) velocities as well as deceleration time (DT) were measured using pulsed-wave Doppler by placing the sample volume at the tips of the mitral leaflets in apical four-chamber view. Isovolumic relaxation time (IVRT) was measured as the time interval from the end of LV outflow and start of LV inflow, as indicated by simultaneous registration of outflow and inflow signals by high-frequency pulsed-wave Doppler.

Pulmonary venous flow (PVF), systolic (S), diastolic (D) and atrial reversal (Ar) velocities were obtained by placing a pulsed-wave Doppler sample volume 1–2 cm into the pulmonary vein, proximal to its insertion into the left atrium. E/A and S/D were calculated.

Diastolic function (DF) was categorised into grades according to its progression to diastolic dysfunction (DD):

- normal DF: E/A between 1 and 2, IVRT 60–100 ms and DT 160–240 ms
- grade 1 DD: E/A < 1, IVRT > 100 ms, DT > 240 ms
- grade 2 DD: E/A 1–2, IVRT 60–100 ms, DT 150–220 ms, PVFS/D < 1
- grade 3 DD: E/A > 2, IVRT < 60 ms, DT < 160 ms

where DT is deceleration time and PVFS is pulmonary venous flow S velocity.

Pulmonary artery systolic pressure (PASP) was estimated from peak tricuspid regurgitant flow using continuous-wave Doppler. Tissue Doppler echocardiography was not used because, at the time the study was conducted, the echo machine used did not have the facility.

Statistical analysis
Data obtained were analysed using STATA 10. Continuous variables are expressed as mean (± standard deviation) and
categorical variables as percentages. Categorical variables were analysed using the chi-squared test. Student’s t-test and analysis of variance (ANOVA) were used to analyse continuous variables. Correlates of LV function were determined using Pearson’s rank correlation and predictors were assessed using logistic regressions. A p-value ≤ 0.05 was considered statistically significant.

Results

One hundred and ninety-three participants comprising 63 T2DM patients with normoalbuminuria, 71 T2DM with microalbuminuria and 59 controls were studied. The mean age for all participants was 50 years and the three groups were age and gender matched. Table 1 shows the clinical characteristics of the three study groups. The duration since diagnosis of DM was significantly longer in the microalbuminuric than in the normoalbuminuric diabetics (p = 0.02). WC, SBP and PR showed a significant stepwise increase from control to microalbuminuric group (p < 0.001, p = 0.03, p = 0.03, respectively). Weight, BMI, WHR, DBP and PP were comparable among the three groups.

Renal function, as assessed by estimated glomerular filtration rate (eGFR) using the Cockcroft Gault formula, was reasonably preserved among the three groups. It was highest in the control group but not statistically significantly different.

The mean values of all lipid components were normal and comparable, except for the low-density lipoprotein (LDL) cholesterol level and atherogenic ratio, which showed a significant stepwise increase from control to microalbuminuric group (p = 0.0008 and p = 0.01, respectively). FBS was also significantly higher in the diabetic groups compared to the controls (p = 0.001).

Table 2 shows the echocardiographic parameters of LV function among the three groups. Mean values of EF and FS were normal in the three groups, but FS showed a significant stepwise decrease from control to microalbuminuric group (p = 0.0002).

Doppler echocardiographic parameters showed some degree of LV diastolic dysfunction, which was more pronounced in the diabetic groups. A velocity (p = 0.0034), IVRT (p = 0.0001) and PASP (p = 0.02) showed a significant stepwise increase from control to microalbuminuric group, with a reverse trend for E velocity (p < 0.001) and E/A ratio (p < 0.001).

Fig. 1 shows the prevalence and pattern of LVDD among the three groups. The prevalence of LVDD showed a stepwise increase from 16.9% in the control to 78.9% in the microalbuminuric group. The most common grade of DD was grade 1, which occurred in 70.4 and 55.5% of microalbuminuric and normoalbuminuric groups, respectively, compared to 16.9% in the controls. Grade 1 was the only type of DD found in the control group; 3.2% of the normoalbuminuric group and 8.5% of the microalbuminuric group had grade 2 pattern of DD. None of the microalbuminuric group had grade 3 but 3.2% of the normoalbuminuric group did. These observed differences were statistically significantly different (χ² = 50.05, p < 0.01).

Table 3 shows clinical and biochemical parameters that correlated significantly with indices of LV diastolic function.
The strongest correlate of E/A ratio in the model was age (p < 0.001). Serum creatinine level (p = 0.009) and eGFR (p = 0.009) also correlated significantly with E/A, but the other parameters did not.

Table 4 shows univariate and multivariate regression models used to determine predictors of LVDD in the normotensive diabetics. At the univariate level, age and MCA status were used to determine predictors of LVDD in the normotensive group. Only age remained an independent predictor of DD. The model, only age remained an independent predictor of DD. The model shows that for every one year increase in age, there was a 10% increased risk of developing DD (OR = 1.10, 95% CI: 1.03–1.17, p = 0.003). The area under the receiver operating curve of this model was 0.76, suggesting a good model.

Discussion

In this study, LVDD occurred significantly more frequently in the diabetic groups with or without MCA compared with the controls (p < 0.001) and the prevalence of LVDD in both diabetic groups were within the range of 40 to 75% reported by studies done on normotensive diabetics within and outside the country. Grade 1 LVDD was the commonest, which was significantly more in the microalbuminuric than the normoalbuminuric group and was the only grade seen in the controls (p < 0.01). Aigbe et al. and Patil et al. reported similar findings. Higher grades (2 and 3), although rare, were commoner in the microalbuminuric (8.5%) than the normoalbuminuric group (6.4%).

Lower rates of LVDD were reported by Liu et al. among American Indians with T2DM, 16% in normo-, 26% in micro- and 31% in the macroalbuminuric groups, because diastolic dysfunction assessment was based on only transmitral flow parameters, with no distinctions made between normal and grade 2 DD. Therefore, patients with a pseudo-normalised pattern were not included in their analysis.

Systolic dysfunction was rare among the normoalbuminuric T2DM patients, which is similar to a previous report. A higher value of 15.56% reported by Dodiyi-Manuel et al. may be due to the higher EF cut-off value of 55% used to define systolic dysfunction, thus suggesting that systolic dysfunction detected by conventional echocardiography is not an early feature of DMCMP. This supports the assumption that alteration of both relaxation and filling usually precede marked changes in chamber systolic function, although more sophisticated imaging technology such as speckle-tracking imaging (STI), used to assess myocardial strain and strain rate, have permitted the detection of subtle systolic dysfunction in the diabetic myocardium.

The significant correlation of E/A ratio with age (p < 0.001), creatinine level (p = 0.009) and eGFR (p = 0.008) in the normotensive T2DM patient suggests a worsening of LVDD.

Table 4. Logistic regression model to determine predictors of left ventricular diastolic dysfunction in the normotensive diabetic subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.11 (1.04–1.17)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>3.58 (1.99–6.82)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Gender</td>
<td>0.69 (0.31–1.55)</td>
<td>0.309</td>
</tr>
<tr>
<td>BMI</td>
<td>0.98 (0.90-1.07)</td>
<td>0.719</td>
</tr>
<tr>
<td>Waist</td>
<td>1.01 (0.98–1.06)</td>
<td>0.452</td>
</tr>
<tr>
<td>DM duration</td>
<td>1.10 (0.96–1.09)</td>
<td>0.142</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>1.01 (0.95–1.05)</td>
<td>0.824</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td>0.96 (0.89–1.03)</td>
<td>0.234</td>
</tr>
</tbody>
</table>

Receiver operating curve 0.76, CI: confidence interval, DM: diabetes mellitus, BP: blood pressure.
as the patient grows older and serum creatinine level rises as a result of decline in renal function. Danbauchi et al.\textsuperscript{10} reported a significant correlation of LVDD with age, fasting blood glucose and two-hour postprandial glucose level in T2DM patients. Likewise, Yazici et al.\textsuperscript{25} in their study on 76 T2DM patients of Turkish origin documented that E/A ratio correlated significantly with age, glycated haemoglobin (HbA\textsubscript{1c}) level and duration of diabetes. These observations suggest that aging and impairment of renal function correlate with LVDD in normotensive diabetics.

The relationship between microalbuminuria and asymptomatic LVDD in T2DM patients has been a subject of much debate. In this study, a worsening of diastolic function as evidenced by significantly higher A velocity, lower E velocity and E/A ratio, larger left atrial dimension and longer IVRT were observed in the microalbuminuric compared to normoalbuminuric group. Baykan et al.\textsuperscript{22} also reported significantly longer deceleration time and IVRT in the microalbuminuric than the normoalbuminuric group.

Liu et al.\textsuperscript{11} was the first to report that albuminuria status was independently associated with systolic and diastolic dysfunction in patients with T2DM. Akiyama et al.\textsuperscript{13} reported that the odds of having LVDD in Japanese T2DM patients with albuminuria was about eight times more than those without albuminuria (OR 7.95, 95% CI: 1.74–21.6, \(p=0.005\)). By contrast, Alwis et al.\textsuperscript{19} noted in their study on 28 T2DM patients without any cardiovascular disease that 73.7% of those without microalbuminuria and 66.7% of those with microalbuminuria had LVDD. Likewise, Yildirimturk et al.\textsuperscript{24} found among 50 diabetics, no significant differences in LV systolic and diastolic function between patients with or without MCA. The relatively smaller sample sizes may explain the lack of significant difference in diastolic function between diabetic patients with or without MCA in these studies.

In our study, the univariate model showed a strong direct association of LVDD with microalbuminuria (OR 3.58, 95% CI: 1.17–10.17, \(p<0.001\)) and age (OR 1.10, 95% CI: 1.03–1.17, \(p=0.001\)), which is similar to a previous study.\textsuperscript{12} Only age remained as an independent predictor of LVDD (OR 1.10, 95% CI: 1.03–1.17, \(p<0.003\)) after controlling for other confounders, including microalbuminuria.

It is commonly believed that grade 1 LVDD in patients above 65 years may represent a relaxation abnormality associated with the aging process. However patients younger than 65 years may represent impaired relaxation due to other conditions, which may be a precursor to more advanced diastolic impairment if not treated. In our study, subjects older than 65 years were excluded. The negative prevalence of grade 2 and 3 LVDD in the control group and the fact that pseudo-normal and restrictive LV filling patterns are usually pathological phenomena\textsuperscript{11} suggest that the higher proportion of LVDD seen in the diabetic groups was linked not only to aging but also to DM with or without MCA.

We included both micro- and macroalbuminuric patients in our study, as this increased the chances of detecting albuminuria as an independent predictor of LVDD, as reported by Liu et al.\textsuperscript{11} in their study. Although the association between MCA and LVDD in normotensive T2DM patients was weak, it was stronger than the association of T2DM without albuminuria with LVDD.

The limitation in this study was lack of glycated haemoglobin values of the subjects studied.

**Conclusion**

Our study showed that the prevalence of LVDD was significantly higher in normotensive T2DM patients with or without microalbuminuria. This study was also confirmatory of the strong direct association of microalbuminuria with LVDD and the direct and independent association of age with LVDD in normotensive diabetic patients. Therefore periodic screening for microalbuminuria, especially in patients with risk factors such as hypertension or diabetes, could allow early identification of cardiovascular disease and help in stratifying overall cardiovascular risk.

**References**

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