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

TT Shogade, IO Essien, UE Ekrikpo, IO Umoh, CT Utin, BC Unadike, JJ Andy

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 ± 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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Exclusion criteria were hypertension (blood pressure $\geq 140/90$ mmHg or use of antihypertensive drugs), age above 65 years, macroalbuminuria, serum creatinine of $\geq 1.5$ 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 centimetres (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 Accoson 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, 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 immunoassay 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 to its progression to diastolic dysfunction (DD):

- grade 3 DD: E/A $< 1$, IVRT $> 100$ ms and DT $> 240$ 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 ($\pm$ 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 $\leq 0.05$ 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 (E/A ratio and IVRT) among the normotensive diabetics. 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 significantly associated with the occurrence of LVDD. Those with microalbuminuria had about a four-fold increased risk of developing LVDD compared to those with normoalbuminuria (95% CI: 1.99–6.82, p < 0.0001). Also, for every one year increase in age, the risk of developing DD increased by 11% (95% CI: 4–17%, p ≤ 0.001).

After adjusting for all the other factors in the multivariate model, only age remained an independent predictor of DD. The model shows that for every one year increase in age, there was...
more in the microalbuminuric than the normoalbuminuric group and was the only grade seen in the controls \((p < 0.01)\). Aigbe et al.\(^6\) and Patil et al.\(^7\) 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.\(^5\) among American Indians with T2DM, 16% in normo-, 26% in micro- and 31% in the macroalbuminuric groups, because diastolic function assessment was based on only transmural 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 normotensive T2DM patients, which is similar to a previous report.\(^1\) A higher value of 15.56% reported by Dodiy-Manuel et al.\(^2\) 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.\(^3\)

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 as the patient grows older and serum creatinine level rises as a result of decline in renal function. Danbauchi et al.\(^4\) reported a significant correlation of LVDD with age, fasting blood glucose and two-hour postprandial glucose level in T2DM patients. Likewise, Yazici et al.\(^31\) in their study on 76 T2DM patients of Turkish origin documented that E/A ratio correlated significantly with age, glycated haemoglobin \((\text{HbA}_1\text{c})\) 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.\(^2\) also reported significantly longer deceleration time and IVRT in the microalbuminuric than the normoalbuminuric group.

![Composite bar chart showing the prevalence and pattern of left ventricular diastolic dysfunction among the three groups.](image-url)

**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\(^4\) and outside the country.\(^7\) Grade 1 LVDD was the commonest, which was significantly

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![Composite bar chart showing the prevalence and pattern of left ventricular diastolic dysfunction among the three groups.](image-url)
Liu et al. was the first to report that albuminuria status was independently associated with systolic and diastolic dysfunction in patients with T2DM. Akiyama et al. 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. 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. 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: 1.99–6.82, p=0.001) and age (OR 1.1, 95% CI: 1.04–1.17, p<0.001), which is similar to a previous study. 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 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. 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


Ten-year fall in blood cholesterol of Malaysia heart attack patients suggests statin impact

A 10-year decline in the blood cholesterol of heart attack patients in Malaysia suggests that statins are having a positive impact, according to an observational study in nearly 49,000 patients presented at the ASEAN Federation of Cardiology Congress 2017 (AFCC2017).

AFCC2017 was hosted by the Brunei Cardiac Society, with the support of the ASEAN Federation of Cardiology, on 3 to 5 November in Brunei Darussalam. Experts from the European Society of Cardiology (ESC) presented a special programme.

‘Lifestyle changes appear to be responsible for falls in blood cholesterol in the general populations of developed nations while statins have reduced cholesterol in patients with heart disease,’ said lead author Dr Sazzli Kasim, Chair, Malaysian Society of Atherosclerosis and Associate Professor of Medicine, University Technology MARA, Shah Alam, Malaysia.

‘Blood cholesterol is still on the rise in the general population of developing countries like Malaysia,’ he continued. ‘This study investigated trends in cholesterol levels in Malaysian patients with acute coronary syndromes.’

The study included 48,851 patients who had an acute coronary syndrome between 2006 and 2015 in Malaysia and were enrolled in the National Cardiovascular Disease Database Acute Coronary Syndrome (NCVD-ACS) registry. This ongoing registry is maintained by the National Heart Association Malaysia with the support of the Ministry of Health Malaysia. Total cholesterol was assessed on entry to the registry.

The researchers examined trends in cholesterol levels of ACS patients over the 10-year period and compared them to previously published values for the entire population. They found a significant trend for declining total cholesterol from 2006 to 2015 in the ACS population ($p = 0.012$). This was opposite to the total cholesterol trend in the Malaysian population.

ACS patients with a history of coronary heart disease had almost twice the declining rate in cholesterol as those with no history of coronary heart disease. When the researchers examined total cholesterol by type of ACS, they found that patients with unstable angina had the lowest total cholesterol level but the steepest rate of decline, followed by patients with non-ST-elevation myocardial infarction and then patients with ST-elevation myocardial infarction.

Dr Kasim said: ‘We found that blood cholesterol levels have been falling in Malaysian patients with acute coronary syndromes, which is the opposite of the national trend.’

‘Since cholesterol levels have increased significantly in the Malaysian population as a whole, it is highly doubtful that lifestyle change is the reason for the declining cholesterol trend we observed in the ACS population,’ he continued.

Dr Kasim said: ‘While this was an observational study and we cannot infer causality, it seems likely that cholesterol levels decreased as a result of lipid-lowering medication such as statins. ACS patients with a history of coronary heart disease, who were more likely to be taking statins, had a more rapid decline in cholesterol levels than those without a history of coronary heart disease.’

He concluded: ‘These results appear to mimic findings from developed countries in previous years and show that the Malaysian population is reaching similar health milestones. The findings also highlight the need to increase awareness of the harm of raised lipid values and the treatment available.’

Dr Ezam Emran, scientific chair of AFCC 2017, said: ‘This large study suggests that statins are being effectively used by heart attack patients in Malaysia. Rising lipid levels in the general population need to be tackled by promoting healthier lifestyles.’

Professor Michel Komajda, a past president of the ESC and course director of the ESC programme in Brunei, said: ‘The benefits of statins for preventing a second heart attack are unequivocal, as highlighted by the 2017 ESC guidelines. Patients should also be encouraged to quit smoking, adopt a healthier diet and be physically active.’

Source: European Society of Cardiology Press Office