Comparison of Cardiovascular Risk in Microalbuminuric and Normoalbuminuric Type 2 Diabetic Patients in Nigeria

Ehimen Phyllis Odum1* and Asuquo Bassey Ene2

1Department of Chemical Pathology, University of Port Harcourt, Rivers State, Nigeria.
2Department of Chemical Pathology, University of Calabar, Cross River State, Nigeria.

Authors’ contributions

This work was carried out in collaboration between both authors. Author EPO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors EPO and ABE managed the analyses of the study. Author ABE managed the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

Aim: To compare cardiovascular risk in microalbuminuric and normoalbuminuric type 2 diabetic patients.

Study Design: Cross-sectional study.

Methodology: Blood pressure, body mass index (BMI), electrolytes, fasting plasma glucose, lipid profile and renal profile were determined in 120 type 2 diabetic patients attending the Medical Outpatient Clinic from January 2017 to August 2017, and in 120 age-matched control subjects. Semi-quantitative determination of microalbuminuria was done using the “MICRAL test” strip. Microalbuminuria was defined as urinary albumin-creatinine ratio (UACR) of 30 – 300 mg/g (3.4-33.9 mg/mmol).

Results: Twenty-seven (22.5%) diabetic patients had microalbuminuria but 93 (77.5%) patients did not have microalbuminuria. Microalbuminuric diabetic patients had significantly longer duration of diabetes, higher mean BMI, higher blood pressure, higher creatinine, lower estimated glomerular

*Corresponding author: E-mail: phyl Dion@yahoo.com;
filtration rate (eGFR), higher urea, higher potassium, higher total cholesterol, higher LDL and lower HDL, as well as higher prevalence of cardiovascular risk factors including hypertension, dyslipidemia, hypercholesterolemia, high LDL and low HDL, compared to diabetics without microalbuminuria.

**Conclusion:** Microalbuminuric patients had more adverse levels and higher prevalence of cardiovascular risk factors compared to normoalbuminuric patients. Microalbuminuria is known to be an adverse prognostic indicator for clinical cardiovascular outcomes and all-cause mortality in diabetic patients.

**Keywords:** Cardiovascular risk; microalbuminuria; normoalbuminuria; type 2 diabetes; diabetic nephropathy; Nigeria.

### 1. INTRODUCTION

Long-standing hyperglycemia is known to be a significant risk factor for the development of diabetic nephropathy [1]. Diabetic nephropathy, also called diabetic kidney disease, is associated with significant cardiovascular risk and is the leading cause of kidney failure worldwide [2,3]. It is the primary cause of morbidity and premature mortality in patients with diabetes mellitus [4] and accounts for a significant reduction in life expectancy of diabetic patients [4,5]. Diabetic nephropathy usually manifests after 10 years' duration of type 1 diabetes, but may be present at diagnosis of type 2 diabetes [1,5]. Persistent microalbuminuria is the earliest sign of diabetic nephropathy and intervention at this stage can retard or reverse the progression of nephropathy [1,2,6].

In Nigeria, several studies have reported the prevalence of microalbuminuria in both newly diagnosed and established type 2 diabetes to vary between 16.1% to 72.6% [6,7]. Diabetic nephropathy may progress from microalbuminuria to macroalbuminuria with progressive loss of glomerular filtration rate (GFR) until end-stage renal disease (ESRD) [1]. Twenty to 40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy and 20 years later, approximately 20% develop end stage renal failure [5,7]. A racial difference in the prevalence of diabetic nephropathy has been observed. African American patients, for instance, have been reported to suffer greater diabetic nephropathy and kidney damage than Caucasian Americans [5]. Risk factors associated with development of microalbuminuria include high blood pressure, hyperglycemia, dyslipidemia, older age, duration of diabetes and smoking [1,4,6]. Microalbuminuria is a marker of generalized microvascular and endothelial damage and thus is also associated with risk factors for vascular disease, which include inflammation and insulin resistance [8,9].

Screening for microalbuminuria should be initiated five years after diagnosis of type 1 diabetes and at diagnosis of type 2 diabetes, and then annually thereafter [1,7]. A spot urine albumin/creatinine ratio, preferably in a first-morning void, correlates well with a 24-hour urine albumin excretion rate and accurately predicts renal events. It is easily administered and is usually the first-line screening test for diabetic patients [1]. Positive results (30 to 300 mg of albumin per g of creatinine) on two of three tests in a six-month period meet the diagnostic criteria for diabetic nephropathy [1]. About 36% of type 2 diabetic patients have renal insufficiency without microalbuminuria or macroalbuminuria, and diabetic nephropathy may also manifest as a decreased glomerular filtration rate or an increased serum creatinine level. Therefore, screening for diabetic nephropathy should also include measurement of serum creatinine and estimation of GFR [1].

Optimizing glycemic control and using an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, both in normotensive and hypertensive diabetics, slow the progression of diabetic nephropathy [1]. It has been shown that the renoprotective and cardioprotective effects are related to the extent to which albuminuria is lowered [10]. Therefore, detection of microalbuminuria as early as possible in the course of the disease is very important [5]. Weight loss, smoking cessation, and decreased dietary protein have also been recommended [1]. The aim of this study is to compare cardiovascular risk in microalbuminuric and normoalbuminuric type 2 diabetic patients.

### 2. METHODOLOGY

#### 2.1 Subjects

The target population included diagnosed type 2 diabetic patients attending the medical outpatient clinic of the University of Port Harcourt Teaching
Hospital (UPTH). Patients with other acute or chronic illnesses and pregnant women were excluded. Control subjects who had no history of cardiovascular disease, diabetes, hypertension, lipid disorders or other acute or chronic condition were drawn from the general public. Approval was obtained from the Ethical Committee of UPTH and informed consent was obtained from all participants. Demographic, social and medical data of participants were assessed with the use of questionnaires.

2.2 Physical Examination

Blood pressure (BP) of each participant was measured with a mercury sphygmomanometer after ten minutes of rest on two occasions and hypertension was defined as a BP equal to or greater than 140/90 mmHg or the use of antihypertensive medication. Participants were weighed bare footed and wearing light clothing on a weighing balance placed on a flat surface. Their heights were measured on a portable collapsible stadiometer and body mass index (BMI = weight/height\(^2\)) was calculated.

2.3 Specimen Collection

After 10-12 hours overnight fast, 10mL of venous blood was taken from the antecubital fossa of participants for the analysis of fasting plasma glucose, lipid profile and renal profile. Plasma was separated from blood cells after centrifugation at 2500 g for 10 minutes, harvested with a clean Pasteur pipette and stored at -20°C. Freshly voided spot mid-stream urine was also collected from each participant in a plain bottle for determination of microalbuminuria.

2.4 Laboratory Analysis

Plasma creatinine concentration was analysed using the modified Jaffe method and the value obtained was used to calculate the estimated glomerular filtration rate (eGFR) of each participant using the Cockcroft-Gault formula: (140 – Age in years) x (Weight in Kg) x (0.85 if female)/ (0.814 x Plasma Creatinine in µmol/L) [11]. Estimation of fasting plasma glucose was done using the colorimetric glucose oxidase method, electrolytes were analysed by ion-selective electrode method, HDL-cholesterol by precipitation technique, total cholesterol and triglyceride by enzymatic method [12,13] while LDL-cholesterol was calculated using the Friedewald's formula (Total cholesterol – (HDL-C) – (Triglyceride/2.2) in mmol/L [13]. Semi-quantitative determination of microalbuminuria was done using the “MICRAL test” strip [14,15].

2.5 Definition of Variables

2.5.1 Microalbuminuria

Urinary albumin-creatinine ratio (UACR) of 30 – 300 mg/g (3.4-33.9 mg/mmol) [15].

2.5.2 Chronic kidney disease (CKD) stages of renal dysfunction

Stage 1: eGFR ≥ 90 ml/min/1.73 m\(^2\) with kidney damage (albuminuria), stage 2: eGFR = 60 – 89.9 ml/min/1.73 m\(^2\) with kidney damage, stage 3: eGFR = 30 – 59.9 ml/min/1.73 m\(^2\), stage 4: eGFR = 15 – 29.9 ml/min/1.73 m\(^2\), stage 5: eGFR < 15 ml/min/1.73 m\(^2\) (end-stage renal failure) [9,11,14].

2.5.3 Dyslipidemia

Any one or more of hypercholesterolemia (plasma total cholesterol ≥ 5.2 mmol/L), hypertriglyceridemia (plasma triglyceride ≥ 1.7 mmol/L), high LDL (plasma LDL-cholesterol ≥ 3.4 mmol/L) and low HDL (plasma HDL-cholesterol < 1.0 mmol/L in men and < 1.3 mmol/L in women) [16].

2.5.4 Type 2 diabetes

Defined as a fasting plasma glucose ≥ 7.0 mmol/L or use of hypoglycemic drugs [17].

2.5.5 Obesity

Defined as BMI ≥ 30 Kg/m\(^2\) [16].

2.6 Statistical Analysis

Data obtained from this study was analysed using the Statistical Package for Social Sciences (SPSS) version 20.0 (SPSS Inc. Chicago, Illinois, U.S.A.). Frequencies and percentages were obtained for categorical variables. Differences in proportions were analyzed using the chi-squared test. The means of continuous variables were compared using unpaired students’ t test and expressed as mean ± standard deviation (SD). P-values less than or equal to 0.05 were taken to be significant in all analyses.

3. RESULTS

There were 120 diabetic patients made up of 58 (48.3%) males and 62 (51.7%) females and 120 age-matched control subjects consisting of 63
(52.5%) males and 57 (47.5%) females. Diabetic patients had an average duration of diabetes of 5.3 (4.4) years. They had significantly higher blood pressure ($P < .001$), higher fasting plasma glucose ($P < .001$), higher LDL ($P = .04$), higher creatinine ($P = .003$), higher urea ($P = .045$), higher uric acid ($P < .001$), lower eGFR ($P < .001$), lower total cholesterol ($P < .001$), higher LDL ($P < .001$) and lower HDL ($P < .01$) than controls (Table 1).

Twenty-seven (22.5%) diabetic patients had microalbuminuria and 93 (77.5%) patients did not have microalbuminuria. Patients with microalbuminuria had significantly longer duration of diabetes ($P < .001$), higher mean BMI ($P = .02$), higher blood pressure ($P = .03$), higher creatinine ($P < .001$), lower eGFR ($P < .001$), higher LDL ($P < .001$), higher eGFR ($P < .001$), lower eGFR ($P < .001$), lower HDL ($P < .001$) and lower sodium ($P = .03$) than controls (Table 1).

Diabetic patients with microalbuminuria also had significantly higher prevalence of hypertension ($P = .003$), dyslipidemia ($P < .001$), hypercholesterolemia ($P < .001$), high LDL ($P < .001$) and low HDL ($P < .001$) respectively than diabetics without microalbuminuria (Table 2).

### Table 1. Comparison between characteristics of diabetic patients and controls

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (n=120)</th>
<th>Controls (n=120)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>52.7 (12.0)</td>
<td>49.9 (12.1)</td>
<td>.07</td>
</tr>
<tr>
<td>Body mass index (Kg/m$^2$)</td>
<td>26.5 (5.0)</td>
<td>25.2 (4.8)</td>
<td>.18</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.2 (20.7)</td>
<td>116.8 (11.0)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>80.5 (11.6)</td>
<td>72.1 (8.5)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>9.8 (4.5)</td>
<td>4.4 (0.7)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.1 (0.6)</td>
<td>1.0 (0.3)</td>
<td>.14</td>
</tr>
<tr>
<td>High density lipoprotein (mmol/L)</td>
<td>1.2 (0.3)</td>
<td>1.5 (0.4)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Low density lipoprotein (mmol/L)</td>
<td>3.1 (1.0)</td>
<td>2.8 (0.6)</td>
<td>.04*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.9 (1.1)</td>
<td>4.6 (0.5)</td>
<td>.27</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>88.8 (24.3)</td>
<td>78.8 (13.3)</td>
<td>.003*</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>87.9 (30.2)</td>
<td>108.6 (28.2)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>4.1 (1.6)</td>
<td>3.7 (1.2)</td>
<td>.045*</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>551.1 (261.0)</td>
<td>250.3 (62.9)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138.8 (3.5)</td>
<td>140.4 (3.9)</td>
<td>.03*</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.0 (0.4)</td>
<td>4.1 (0.5)</td>
<td>.43</td>
</tr>
</tbody>
</table>

* $P$-values $\leq .05$ significant; $n$ – number; SD – Standard deviation

### Table 2. Characteristics of diabetic patients with and without microalbuminuria

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (SD)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.3 (11.1)</td>
<td>.21</td>
</tr>
<tr>
<td>Duration of Diabetes (Years)</td>
<td>10.6 (4.7)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Body mass index (Kg/m$^2$)</td>
<td>28.9 (5.6)</td>
<td>.02*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>137.1 (17.8)</td>
<td>.03*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.5 (11.5)</td>
<td>.03*</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/L)</td>
<td>9.6 (5.1)</td>
<td>.89</td>
</tr>
<tr>
<td>Triglyceride (mmol/L)</td>
<td>1.2 (0.5)</td>
<td>.40</td>
</tr>
<tr>
<td>High density lipoprotein (mmol/L)</td>
<td>1.1 (0.3)</td>
<td>.01*</td>
</tr>
<tr>
<td>Low density lipoprotein (mmol/L)</td>
<td>4.2 (1.2)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>5.8 (1.3)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>114.0 (17.8)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>eGFR (ml/min)</td>
<td>70.4 (25.2)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>4.8 (1.1)</td>
<td>.004*</td>
</tr>
<tr>
<td>Uric acid (mmol/L)</td>
<td>558.5 (269.8)</td>
<td>.89</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>139.8 (2.2)</td>
<td>.17</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.3 (0.4)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

* $P$-values $\leq .05$ significant; $n$ – number; SD – Standard deviation
Table 3. Prevalence of cardiovascular risk factors in diabetic patients stratified by the presence of microalbuminuria

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Microalbuminuric Patients (n=27)</th>
<th>Normoalbuminuric Patients (n=93)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>18 (66.7)</td>
<td>30 (32.3)</td>
<td>.003*</td>
</tr>
<tr>
<td>Obesity</td>
<td>8 (29.6)</td>
<td>14 (15.1)</td>
<td>.15</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (85.2)</td>
<td>31 (33.3)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>22 (81.5)</td>
<td>14 (15.1)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>5 (18.5)</td>
<td>10 (10.8)</td>
<td>.46</td>
</tr>
<tr>
<td>Low HDL</td>
<td>16 (59.3)</td>
<td>17 (18.3)</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>High LDL</td>
<td>24 (88.9)</td>
<td>16 (17.2)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

* P-values ≤ .05 significant; n – number; SD – Standard deviation

4. DISCUSSION

Ogbu et al. recorded a prevalence of 16.1% for microalbuminuria among diabetic patients in Enugu [18]. This percentage is lower than the 22.5% obtained in this study. Higher prevalences of 58.0% and 72.6% were reported in Warri and Benin respectively [6,7]. Patients with microalbuminuria had longer duration of diabetes. Similar findings have been observed in previous studies which revealed that duration of diabetes correlates positively with prevalence of microalbuminuria and has been identified as a strong predictor for development of albuminuria in Type 2 diabetic patients [5,6]. Microalbuminuric diabetic patients had higher BMI, higher blood pressure and more adverse lipid and renal profiles, as well as higher prevalence of cardiovascular risk factors including hypertension, dyslipidemia, hypercholesterolemia, high LDL and low HDL compared to diabetics without microalbuminuria. Diabetics with microalbuminuria have been shown to have ahigher prevalence of traditional risk factors than diabetics without microalbuminuria [9].

Microalbuminuria reflects greater severity of end organ damage [9]. It is an early predictor of progressive renal function loss and development of overt diabetic nephropathy in diabetes [8,10,20]. At the time that microalbuminuria becomes manifest, glomerular filtration rate typically is normal or elevated or only modestly impaired (CKD stage 1 or 2) [3,10]. Individuals with macroalbuminuria most likely are already in CKD stage 3 or 4 [3,10]. The incidence and severity of cardiovascular morbidity and mortality are known to increase as glomerular filtration rate declines [22]. Diabetics in this study were observed to have poorer renal function than healthy individuals, and this was further aggravated in microalbuminuric diabetics compared to normoalbuminuric diabetics. Similar findings were documented by Jisieike-Onuigbo et al. [3].

Dyslipidemia is also more prevalent in diabetics than healthy subjects, and also in albuminuric diabetics than patients without albuminuria, as observed in this study. The most common pattern of dyslipidemia in diabetic patients consists of elevated levels of serum triglyceride and low levels of HDL-C [3]. However, high levels of total cholesterol and LDL-C, and low levels of HDL-C were seen in this study. In diabetes, the predominant form of LDL cholesterol is the small, dense form. Small LDL particles are more atherogenic than large LDL particles because they can more easily penetrate and form stronger attachments to the arterial wall, and they are more susceptible to oxidation [21]. Dyslipidemia is highly correlated with atherosclerosis [21] and previous studies have shown conclusively that lipid abnormalities in patients with diabetes mellitus are associated with increased risk of cardiovascular disease [3].

Elevated blood pressure is documented as the most significant contributing factor in the etiology of microangiopathy [7], pathogenesis and progression of albuminuria and eventually, development of diabetic nephropathy in type 2 diabetic patients [5]. Hypertension in type 2 diabetes may be partly a consequence of insulin resistance and of hyperinsulinemia [19]. Arterial pressure, mainly systolic arterial pressure (SAP) and to a lesser extent pulse pressure, is a major determinant of albuminuria and has been linked to the degree and severity of diabetic nephropathy [20]. Hypertension is about twice as frequent in diabetic patients as in non-diabetic subjects [8,19]. Diabetic patients in this study had higher blood pressure than controls and the prevalence of hypertension among microalbuminuric patients was double that of normoalbuminuric patients.
Microalbuminuria is as potent a risk factor for cardiovascular events as a previous history of actual cardiovascular disease [20]. Evidence suggests that as the amount of urinary albumin excretion increases along the continuum from microalbuminuria to macroalbuminuria and proteinuria, the risk of adverse cardiovascular events increases [20]. Several studies have shown that reduction of albuminuria by inhibition of the renin-angiotensin-aldosterone system is associated with the preservation of renal function and reduced risk of adverse cardiovascular events [8,10,20].

5. CONCLUSION

Microalbuminuric diabetic patients had more adverse clinical, lipid and renal profiles, and higher prevalence of cardiovascular risk factors including hypertension, dyslipidemia, hypercholesterolemia, high LDL and low HDL than normoalbuminuric diabetics. Microalbuminuria is associated with increased risk of major cardiovascular events and all-cause mortality. Early detection and treatment and lifestyle adjustments have been shown to halt the progression from microalbuminuria to macroalbuminuria and eventually end-stage renal failure.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for this study.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES