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Original Research Article

Microalbuminuria as an early predictor of cardiovascular risk in type 2 diabetic patients

ABSTRACT

Aim: To screen for microalbuminuria in type 2 diabetic patients and determine its association with cardiovascular risk factors.

Study Design: Cross-sectional study

Place and Duration of Study: Medical Outpatient Clinic, Department of Internal Medicine, University of Port Harcourt Teaching Hospital, Rivers State, Nigeria from January 2017 to August 2017.

Methodology

Fasting plasma glucose, lipid profile and renal profile were determined in 120 type 2 diabetic patients and 120 age-matched control subjects. Semi-quantitative determination of microalbuminuria was done using the "MICRAL test" strip.

Results

Twenty-seven (22.5%) diabetic patients had microalbuminuria but 93 (77.5%) patients did not have microalbuminuria. Microalbuminuric diabetic patients were more obese, had higher blood pressure and more adverse lipid and renal profiles, as well as higher prevalence of 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. Early detection and treatment of microalbuminuria are important in order to retard the progression to end stage renal failure and prevent adverse cardiovascular outcomes.

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Keywords: Microalbuminuria, early predictor, cardiovascular risk, type 2 diabetes, diabetic nephropathy

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]. Diabetic nephropathy usually manifests after 10 years' duration of type 1 diabetes, but may be present at diagnosis of type 2 diabetes [1]. 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

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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 screen for microalbuminuria in type 2 diabetic patients and determine its association with cardiovascular risk factors.

2. METHODOLOGY

2.1 Subjects

The target population included diagnosed asymptomatic type 2 diabetic patients of 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 taken as a BP equal to or greater than 140/90 mmHg. Participants were weighed bare footed and wearing light clothing on a weighing balance placed

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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 2500g for 10 minutes, harvested with a clean Pasteur pipette and stored at -20^{0}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, HDL-cholesterol by precipitation technique, total cholesterol and triglyceride by enzymatic method [12] while LDL-cholesterol was calculated using the Friedewald's formula [13]. Semi-quantitative determination of microalbuminuria was done using the "MICRAL test" strip [14].

2.5 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.

2.6 Definition of Variables

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

Chronic Kidney Disease (CKD) Stages of renal dysfunction: Stage 1: eGFR ≥ 90 ml/min/1.73 m^2 with kidney damage, stage 2: eGFR = 60 – 89.9 ml/min/1.73 m^2 with kidney damage, stage 3: eGFR = 30 –

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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 [9,11].

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].

Type 2 diabetes: Defined as a fasting plasma glucose ≥ 7.0 mmol/L [17].

Obesity: Defined as BMI ≥ 30 Kg/m^2 [16].

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 HDL (P < .001) and lower sodium (P = .03) than controls (Table 1).

Table 1: Comparison between characteristics of diabetic patients and controls

Characteristic	Mean (SD)		*P*
	Patients (n=120)	Controls (n=120)	
Age (years)	52.7 (12.0)	49.9 (12.1)	.07
Body mass index (Kg/m^2)	26.5 (5.0)	25.2 (4.8)	.18
Systolic blood pressure (mmHg)	129.2 (20.7)	116.8 (11.0)	<.001*
Diastolic blood pressure (mmHg)	80.5 (11.6)	72.1 (8.5)	<.001*
Fasting plasma glucose(mmol/L)	9.8 (4.5)	4.4 (0.7)	<.001*
Triglyceride (mmol/L)	1.1 (0.6)	1.0 (0.3)	.14
High density lipoprotein (mmol/L)	1.2 (0.3)	1.5 (0.4)	<.001*
Low density lipoprotein (mmol/L)	3.1 (1.0)	2.8 (0.6)	.04*
Total cholesterol (mmol/L)	4.9 (1.1)	4.6 (0.5)	.27
Creatinine (µmol/L)	88.8 (24.3)	78.8 (13.3)	.003*
eGFR (ml/min)	87.9 (30.2)	108.6 (28.2)	<.001*

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Urea (mmol/L)	4.1 (1.6)	3.7 (1.2)	.045*
Uric acid (mmol/L)	551.1 (261.0)	250.3 (62.9)	<.001*
Sodium (mmol/L)	138.8 (3.5)	140.4 (3.9)	.03*
Potassium (mmol/L)	4.0 (0.4)	4.1 (0.5)	.43

* *P*-values ≤ .05 significant

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 urea ($P = .004$), higher potassium ($P < .001$), higher total cholesterol ($P < .001$), higher LDL ($P < .001$) and lower HDL ($P < .01$) than diabetics without microalbuminuria (Table 2).

Table 2: Characteristics of diabetic patients with and without microalbuminuria

Variable	**Mean (SD)**		***P***
	Microalbuminuric Patients (n=27)	**Normoalbuminuric Patients (n=93)**	
Age (years)	55.3 (11.1)	51.4 (13.4)	.21
Duration of Diabetes (Years)	10.6 (4.7)	3.8 (3.0)	<.001*
Body mass index (Kg/m^2)	28.9 (5.6)	25.5 (5.3)	.02*
Systolic blood pressure (mmHg)	137.1 (17.8)	126.3 (20.5)	.03*
Diastolic blood pressure (mmHg)	85.5 (11.5)	78.8 (11.6)	.03*
Fasting plasma glucose(mmol/L)	9.6 (5.1)	9.8 (4.2)	.89
Triglyceride (mmol/L)	1.2 (0.5)	1.1 (0.6)	.40
High density lipoprotein (mmol/L)	1.1 (0.3)	1.3 (0.3)	.01*
Low density lipoprotein (mmol/L)	4.2 (1.2)	2.8 (0.7)	<.001*
Total cholesterol (mmol/L)	5.8 (1.3)	4.5 (0.8)	<.001*
Creatinine (µmol/L)	114.0 (17.8)	79.8 (19.6)	<.001*
eGFR (ml/min)	70.4 (25.2)	94.1 (29.6)	<.001*
Urea (mmol/L)	4.8 (1.1)	3.8 (1.7)	.004*
Uric acid (mmol/L)	558.5 (269.8)	548.4 (260.2)	.89
Sodium (mmol/L)	139.8 (2.2)	138.8 (3.7)	.17
Potassium (mmol/L)	4.3 (0.4)	3.9 (0.4)	<.001*

* *P*-values ≤ .05 significant

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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 3).

Table 3: Prevalence of cardiovascular risk factors in diabetic patients stratified by the presence of microalbuminuria

Risk Factor Frequency (%)	Microalbuminuric Patients (n=27)	Normoalbuminuric Patients (n=93)	*P*
Hypertension	18 (66.7)	30 (32.3)	.003*
Obesity	8 (29.6)	14 (15.1)	.15
Dyslipidemia	23 (85.2)	31 (33.3)	<.001*
Hypercholesterolemia	22 (81.5)	14 (15.1)	<.001*
Hypertriglyceridemia	5 (18.5)	10 (10.8)	.46
Low HDL	16 (59.3)	17 (18.3)	<.001*
High LDL	24 (88.9)	16 (17.2)	<.001*

* *P*-values ≤ .05 significant

4. DISCUSSION

Twenty-seven (22.5%) diabetic patients had microalbuminuria. Ogbu et al recorded a lower prevalence of 16.1% in Enugu [18]. Higher prevalences were reported in Warri and Benin [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 were more obese, had 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 a higher prevalence of traditional risk factors than diabetics without microalbuminuria [9].

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

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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.

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].

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].

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

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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. A copy of the written consent is available for review by the editorial office/chief editor/editorial board members of this journal.

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.

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