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Microalbuminuria in controlled Type 2 diabetes mellitus patients

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Summary
Microalbuminuria assessment using albumin: creatinine ratio (ACR) by ELISA in early morning urine sample was studied in 83 (43 males, 40 females) normotensive type 2 diabetic patients and 40 (20 males; 15 females) age matched apparently healthy control subjects attending the medical outpatient clinic of the University College Hospital, Ibadan. The prevalence of microalbuminuria among the diabetic patients was found to be 60% and 30% among the controls. The level of microalbuminuria was found to correlate with age, duration of diabetes, blood pressure and waist:hip ratio. In both the patients and the controls, microalbuminuria was uncommon below the age of 50 years. The study highlights the contribution of a background renal insult as the probable reason for the high prevalence of microalbuminuria.

Keywords: *Prevalence, microalbuminuria, albumin : creatinine ratio (ACR), Type 2 DM.*

Résumé
L'évaluation microalbuminurie en employant la proportion creatinine d'albumine (PCA) par ELISA dans une prise d'urine martinale était étudié dans 83 (43 hommes, 40 femmes) malades diabetiques normotensives de 2ème type et 40(20 hommes; 15 femmes) sujets de contrôle en bonne santé qui assistent la clinique de consultation externe dans l'hospitalier universitaire d'Ibadan. La fréquence de microalbuminuria parmi les malades diabétiques était 60% et 30% au groupe de contrôle. Le niveau de microalbuminuria était en corrélation avec l'âge, la durée de diabète, la pression de sang, et la proportion de taille:hanche. Dans ces deux groupes des malades et des contrôles, le microalbuminuria était peu commun pour ceux dont leur âges sont moins de 50ans. L'étude souligne la contribution d'expérience d'abus rénal comme la cause la plus possible pour une haute fréquence de microalbuminuria.

Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterised by hyperglycaemia resulting from defects in insulin secretion, insulin action or both [1]. The chronic hyperglycaemia of diabetes is associated with dysfunction and failure of various organs and is the most common single cause of end stage renal disease (ESRD) in the United States of America and Europe [2] as well as in Nigeria [3-7].

The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels of albumin in the urine known as microalbuminuria. Microalbuminuria is defined as albumin excretion >30 – 300mg/24h or 20 - 200μg/min [2, 8] for timed urine collection. Data on the prevalence of microalbuminuria in Nigeria is not available but elsewhere prevalence of 20.8–34% have been reported [9, 10-13] in population based studies. With the prevalence of diabetes on the increase in Nigeria, the prevalence of microalbuminuria and the associated complications will also be on the increase. Without specific intervention 20–40% of type 2 diabetic patients with microalbuminuria progress to overt nephropathy over a 10–15 year period [2]. Identification and treatment of DM patients at high risk of developing nephropathy has been shown to be possible by screening for microalbuminuria. Regular screening for microalbuminuria will therefore delay or prevent nephropathy and improve the quality of life of such patients.

This study was therefore carried out to screen diabetic patients in this environment with the aim of knowing the prevalence of microalbuminuria and the contributory role or otherwise of age, glycaemic control and body mass index.

Materials and methods

Subjects

Eighty-three (43 males, 40 females) consecutive normotensive (BP < 140/90) age range 30 –74 years type 2 diabetic patients attending the medical out-patient department clinic of the University College Hospital, Ibadan, were recruited for the study. Informed consent was obtained from every patient controlled either on diet or oral hypoglycaemic agents or both. Forty (25 males, 15 females) apparently healthy controls aged 31–75 years were also studied. At screening, these patients as well as the controls were albustix negative. The control subjects were normotensive and had fasting blood glucose values below 5 mmol/L.

Urinary tract infection in the subjects and the controls was excluded by urine microscopy where greater than 5 white blood cells per high power field was regarded as significant bacteriuria. Patients with febrile illness, pregnancy and evidence of cardiac decompensation were excluded from the study.

Materials

Mid-stream clean catch urine sample was collected in a clean sterile universal bottle between 8 and 9 a.m. The urine sample was immediately tested for protein using albustix (Bayer Diagnostic Division U.S.A) which has a detection limit of greater than 0.3g/dL (1+). Microscopy was then done to exclude UTI. Samples found to be negative were then stored at 4°C until batch analysis for microalbuminuria and creatinine was done within 8 weeks of collection.

Blood glucose

Fasting whole blood glucose results from the last three previous visits were retrieved from the case notes of the diabetic patients. They were collated and the average was taken as an index of aggregate glycaemic control which was then classified as poor, fair or good based on WHO 1985 [14] recommendation, i.e., Good (2.5 – 5.0mmol/L), fair (>5.0 – 6.7mmol/L) and poor (> 6.7mmol/L). The control subjects had fasting blood glucose done on one occasion to determine that they were not diabetic.

Methods

A pre-tested and validated questionnaire was administered on each of the patients and control subjects that satisfied the inclusion criteria. The questionnaire documented the respondents bio data, anthropometric measurements and diabetic history ir the subjects.

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Blood pressure was recorded sitting and back supported using mercury sphygmomanometer at the right arm at the level of the heart after 10 minutes of rest. The systolic pressure was taken when sound was first heard clearly (phase 1) and the diastolic pressure at the level at which the sound disappeared (phase v). Two records were taken for each patient at intervals of 5 minutes with appropriate size cuff, the average was used for analysis. The subjects had not smoked or ingested caffeine during the previous 30 minutes.

Laboratory method

Urinary albumin was determined in batches by competitive enzyme-linked immunosorbent assay (ELISA) [Randox Laboratories Ltd. Ardmore U. K.].
Intra assay CV = 8.1% at 6mg/L and 6.9% at 12/mg/L
Inter assay CV = 8.0% at 6mg/L and 9% at 12/mg/L.

Urinary creatinine was determined by Jaffe's reaction [15] blood glucose determination was done using the glucose oxidase method [15].

Albumin : creatinine ratio (ACR) for each patient and control subjects was determined as follows:
Albumin in mg/L = ( )mg/mmol.
Creatinine in mmol/L

Microalbuminuria in terms of albumin : creatinine ratio was defined as follows.[16]

	ACR (mg/mmol)		
Gender	Normal	Microalbuminuria	Gross
Male	ACR < 2.5	2.5 – 25	> 25
Female	ACR < 3.0	3.0 – 30	> 30

This study was approved by the Joint UI/UCH Ethical Review Committee.

Statistical analysis

Statistical analysis used in this study are the student's t test and Kruskal Wallis test. P value significance was fixed at 0.05.

Results

A total of 123 subjects comprising 83 patients and 40 controls were studied. The mean age and ranges were comparable in the two groups (Table 1).

Table 1: Comparable features in type 2 DM patients and the controls [mean (SD)].

	Type 2 DM n = 83	Controls n = 40
Age	54.7 (35-74)*	52.3 (31-75)*
Height (SD) (m)	1.66 (0.1)	1.67 (0.1)
Systolic BP (SD) (mmHg)	122.3 (12.9)	117.3(12.8)
Diastolic BP (SD) (mmHg)	77.4 (7.4)	76.8 (6.3)
MAP (SD) (mmHg)	92.4 (7.9)	90.3 (7.2)
Urinary Creatinine (SD) (mmol/L)	0.79 (0.4)	0.81 (0.3)

**Range MAP-Mean Arterial Pressure*
P is >0.05 (i.e not significant) in all these variables

The variables of height and systolic blood pressure were not significantly different in the two groups, while the weight, BMI and albumin:creatinine ratio differ significantly Tables 1 and 2.

Table 2: Comparison of weight, BMI, FBG and ACR in the diabetic and the controls [Mean (SD)]

Variables	Type 2 DM n = 83	Controls n = 40
Weight (SD) (kg)	70.1 (11.8)	63.6 (10.1)
BMI (SD) (kg.m^2)	25.4 (14.9)	23.1 (4.2)
Aggregate FBG (SD) mmol/L	7.37 (3.98)	3.86 (0.52)
ACR (SD) (mg/mmol)	14.28 (20.9)	4.38 (4.7)

$P < 0.05$ i.e. significant in all these variables

Microalbuminuria was found to progress with increasing age in the diabetic patients (Table 3). Microalbuminuria occurred in 60% (48 out of 83) of the diabetic subjects while 30% (12 out 40) of control subjects were found to have microalbuminuria. The mean duration of DM was 6.6 years and microalbuminuria worsened with increase in duration of diabetes and with age (Table 3).

Table 3: Mean age of occurrence of proteinuria in the study group

Albumin Excretion (no)	Mean Ages (SD)	Mean Duration Years (SD)
Normal (21)	48.9 (9)*	4.86 (5.4)
Microalbuminuria (48)	54.1 (11.5)*	6.6 (7.4)
Gross Proteinuria (14)	65.5 (9.4)*	8.2 (6.4)

** $P < 0.05$ i.e. significant*

Discussion

Microalbuminuria is the earliest laboratory evidence of incipient diabetic nephropathy [8] It has been appreciated for more than a decade that microalbuminuria predicts risk of progression to overt proteinuria and nephropathy in both type 1 and type 2 diabetics [2,17-19] .The occurrence of microalbuminuria in the type 2 diabetic patients screened in this study using albumin creatinine ratio is 60%. This compares well with 59% reported by Schnack *et al* [20] in a hospital based screening of type II diabetic patients but higher than a prevalence of 20.8 – 34% reported elsewhere in population based studies [9-13]. This was not significantly different from the controls with microalbminuria prevalence of 30%. Several possibilities could be advanced to explain this finding. Parving [13] reported that 27% of the Nigerian type 2 diabetic patients studied were found to have a variety of non-diabetic glomerulopathies on kidney biopsy which could add to the burden of diabetic nephropathy. The possibility of background mild or subclinical glomerulopathies exist among Nigerians based on various immune complex reaction and infective processes in the environment. However the control subjects were apparently healthy at the time of urine collection. Renal biopsy would have further characterised this picture but this was beyond the scope of the study.

Intermittent proteinuria has been known to occur in normotensive individuals [21-23] particularly with high fever, [24–27] strenuous exercise, [28] exposure to cold, [28] emotional stress [29], congestive cardiac failure and essential hypertension [25, 30]. While some conditions such as congestive cardiac failure and essential hypertension have been ruled out, the same cannot be said for the others. That is why several measurements are recommended before aggressive treatment.

Recurrent urinary tract infections, which have been treated in the past especially among the elderly may contribute to the occurrence of microalbuminuria. However all the patients and controls enrolled for the study were albustix negative and most of them did not have significant bacterial count on microscopy. Nonetheless, antibiotics such as cephalosporins and aminoglycosides used to treat urinary tract infection can lead to kidney damage [31] which again may have occurred in these patients and controls. Central to the development of diabetic nephropathy is the structural damage to the glomerular vasculature [8]. The factors associated with predilection to the development of diabetic nephropathy include age at onset, duration of diabetes, drug compliance, degree of metabolic controll [32,33] type of diabetes and race [34,35,8]. Age was found to correlate positively with microalbuminria in this study. In both the patients and the control groups, microalbuminuria was uncommon before the age of 50 years. Furthermore, the prevalence of microalbuminuria was found to increase with age. Diabetic nephropathy characterised by microalbuminuria usually does not occur until about 7 – 15 years after the onset of diabetes [8]. In this study, the mean duration of diabetes is 6.6 years (range 1 month – 30 years). However diabetes may have been present earlier than the duration volunteered by the subjects. Some of the patients could be of the 8% of the population that present with proteinuria at diagnosis of diabetes.

The subtle influence of good glycaemic control on the development of microalbuminuria had been stressed [36]. When poor glycaemic control is prolonged, the rate of formation of glycosylated end products increase [37]. This study used aggregate glycaemic control although glycated haemoglobin technique could have given a better correlation of glycaemic control within the previous 3 months.

Several workers have found albumin : creatine ratio to be of equal diagnostic value to albumin excretion rates [38-41]. There is a significantly higher urinary albumin excretion and albumin : creatinine ratio (ACR) among the diabetics. While the type 2 DM, patients recorded mean ACR of 14.28mg/mmol the controls only had 4.38mg/mmol, indicating that diabetes had probably worsened the kidney function (Table 2). There was no significant difference in ACR and urinary albumin excretion between the male and the female subjects studied.

Our inability to examine for retinopathy in our diabetic subjects did not allow us to correlate retinopathy with our findings. There is a concordance rate of 63% of retinopathy with proteinuria in type 2 diabetes [13].

This study has highlighted the high prevalence of microalbuminuria among Nigerians, a finding which underscores the need for a tight glycaemic control and at least a yearly screening of our diabetic population for microalbuminuria.

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