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NEPHROPATHY IN PATIENTS WITH RECENTLY DIAGNOSED TYPE 2 DIABETES MELLITUS IN BLACK AFRICANS

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ABSTRACT

Background: **Albuminuria is long recognised as a sign of renal disease in diabetes. In type 1 diabetes, renal disease occurs after a longer duration of diabetic state. In type 2 diabetes, it is more variable.**

Objective: **To determine the prevalence and any risk factors of albuminuria in short-term (≤2 yrs) type 2 diabetes.**

Design: **Cross sectional, descriptive study. Microalbuminuria was assessed using micro II strips.**

Setting: **Outpatient diabetic clinic at Kenyatta National Hospital, Nairobi.**

Subjects: **Patients who were newly diagnosed or had had type 2 diabetes for two years or less.**

Main outcome measures: **Microalbuminuria, lipids, glycated haemoglobin, fasting blood glucose and blood pressure.**

Results: **One hundred and thirty nine patients who had type 2 diabetes mellitus for ≤2 yrs were seen, but only 100 patients were included in the study over a six month period. Their mean (SD) age was 53.7 (9.3) years. Mean (SD) duration of diabetes was 10.3 (7.5) months. Fifty per cent of the study patients were hypertensive. Only 48% had HbAlc <8% while 36% had HbAlc >9%. The lipid profile of total, LDL - HDL-cholesterol and triglycerides were predominantly within normal limits. Twenty six per cent were established to have albuminuria of which one patient had macroalbuminuria. Blood pressure, glycated haemoglobin and lipid parameters were not significantly different from patients without albuminuria**

Conclusion: **Albuminuria occurred in a significant proportion of patients with short term type 2 diabetes. Comparable to studies done elsewhere on short-term type 2 diabetes, albuminuria is both a sign of nephropathy and a cardiovascular risk factor. It should be looked for in all patients with type 2 diabetes attending this clinic, even at diagnosis.**

INTRODUCTION

Diabetic nephropathy is a clinical syndrome characterised by persistent proteinuria with a relentless decline in glomerular filtration rate(1). The additional clinical criteria for definition include presence of diabetic retinopathy and no clinical or laboratory evidence of kidney or urinary tract infection other than diabetic glomerulosclerosis(2,3). This clinical definition of diabetic nephropathy is reported to be valid in both insulin independent diabetes mellitus and non-insulin independent diabetes mellitus(2,4).

In type 1 diabetes of recent onset, glomerular filtration rate (GFR) and renal blood flow (RBF) are usually elevated and return towards normal range with improved metabolic control(5). The situation in type 2 diabetes is considerably less clear. Schmitz *et al.* (6) found that GFR was within higher normal range in recently diagnosed patients and decreased to within normal range or even lower levels with good metabolic control.

Diabetic nephropathy may be related to difference in quality of care(7,8), a point that may be very valid in this region where resources are scarce and there is inequity in distribution of care centres.

The rate of decline of renal function has been found to be proportional to the severity of proteinuria, with patients with very heavy proteinuria having the worst prognosis(9). There is paucity of data in black Africa where prevalence of type 2 diabetes mellitus is increasing manifold(10). Consequently diabetic nephropathy is expected to increase proportionately. Erasmus *et al.*(11) have recently reported on hypertension, proteinuria and renal insufficiency in black South Africans with Type 2 diabetes. Their mean duration of disease in the population was 7.8 years. We

examined a cohort of patients of recently diagnosed type 2 diabetes who were consecutively seen at the outpatient diabetic clinic at Kenyatta National Hospital. The aim of this study was to highlight the clinico-laboratory characteristics of the patients with albuminuria and the relationships thereof.

MATERIALS AND METHODS

For each of the 139 consecutive patients recruited, a history was obtained. This included demographic data pertaining to current age, gender, age at diagnosis, usual residence, level of formal education and occupation. Where possible age was confirmed with national identity card but in some cases where this was not possible, an estimate of age from the clinic records was sometimes used. In the medical history, attention was paid to prior diagnosis of hypertension treatment with antihypertensive agents.

A physical examination was then carried out. Weight was measured to the nearest half kilogram(kg) with the patient in light clothing but without shoes using a standard weighing chair in the clinic. The height was measured against a vertical scale with the patient having no shoes, and recorded to the nearest centimetre (cm). Waist circumference was measured as the minimum circumference between the costal margins and the iliac crests while the hip circumference was taken as the circumference measured at the level of the greater trochanteric prominences. Where these were not palpable then the greatest gluteal circumference was measured. The circumferences were both measured. The circumferences were both measured to the nearest millimetre. The body Mass Index (BMI) was then determined as:
(BMI)= Weight (Kg)/Height $(m)^2$ and degree of obesity classified(12).

Blood pressure was measured on the right arm with the patient in sitting position after a rest period of five minutes by the normal manual technique using an adult cuff. Systolic blood pressure was recorded on the appearance of the first sounds (Korotkoff phase 1) while the diastolic pressure corresponded to the disappearance of the sounds (phase 5). Two such readings taken from the top of the meniscus and expressed to the nearest 2mmHg. The mean of the two readings of blood pressure was used for final record.

Assessment of retinopathy was undertaken by an ophthalmologist using direct ophthalmoscopy with dilated pupils using 1% cyclopentolate eye drops. The retinal changes were classified as normal background, pre-proliferative retinopathy and proliferative retinopathy. The cost of retinal fluorescein angiography was too high to allow its use in this screening exercise.

The assessment of nephropathy was done on an early morning, first urine sample of 10mls. A dipstick urinalysis was performed noting the presence of ketones and indices of infections like leucocytes and nitrites. If the latter two were present then the patient was considered to have a urinary tract infection and any albuminuria detected regarded as infection-related. Such patient was then referred for urine microscopy culture and sensitivity tests and the appropriate treatment offered.The microalbuminuria was determined in non-infected urine using Micral-II strips, which gave semi-quantitative values of albuminuria as nil. 20mg/l, 50mg/l and 100mg/l.

All patients were examined in the morning following an overnight fast of minimum 10 hours. Venous blood samples from antecubital fossa were obtained for fasting blood sugar on a 2mls fluoride sample. Three millilitre sample was placed in an ETDA bottle for HbAlc assay while another 5mls was put in a plain bottle for fasting lipid profile and serum creatinine levels.

Predicted creatinine clearance was calculated from the serum creatinine clearance was calculated from the serum creatinine value assayed, using a modified cockroft formula(13) as follows:

Male:

$$\text{Creatinine clearance in ml/per min per 70 kg} = \frac{(145 - \text{age in years}) - 3}{\text{Serum creatinine in mg/dl}}$$

Female:

$$\text{Creatinine clearance ml/min per 70 kg} = \frac{0.85\ (145 - \text{age in years})-3}{\text{Serum creatinine in mg/dl}}$$

HbAlc was assayed using boronic acid capture method and the degree of glycaemic control classified as(14).

≤7% = ideal	8-9% = fair/intermediate
7.1-7.95 = good	>9% = poor

This is the guide on glycaemic control quoted on the manufacturer's brochure the HbAlc kit used, and it is in keeping with the American guildelines on the standards of care(14).

Fasting blood sugar was also assessed and levels categorised as:

≤5.9mmol/l = Ideal	8-8.9mmol/l = fair
6-7.9mmol = good	>10mmol = poor

Lipidaemia was assayed using the cholesterol oxidase and esterase calometric methods. Total cholesterol, HDL cholesterol and triglycerides were determined directly, while LDL-C was derived using Friedwalds' formula(15).

Data analysis

Data were entered into a data analysis proforma, coded and entered into the SPSS computer software system. All statistical analyses were was carried out using the same system. Means and standard deviations were calculated and any statistical significance between different groups were determined by the Mann-Whitney U test. Association between the complications and proposed risk factors was calculated using, the Chi-square Pearson's test.

RESULTS

One hundred and thirty nine patients were seen between June 2000 - Jan 2001. Twenty eight of them failed to honour appointments for unknown reasons and lost to re-evaluation and one did not fulfil the criteria for inclusion because she had urinaly tract infection. Of the remaining 110 patients seen, ten were excluded from analysis because of incomplete data. Below are summary of clinical characteristics of the 100 patients who had complete data (Table 1) and laboratory findings (Table 2).

Table 1

Patient characteristics

Proportion M/F (%)	37/63
Mean (SD) age (yrs)	53.7 (9.3)
Range of age (yrs)	34-80
Mean (SD) duration of diabetes in months	10.3 (7.5)
Positive familly history of hypertension	25%
Proportion of patients with hypertension	50%
Smoking history amongst patients included	73%
BMI (SD) kg/m^2-Population mean	27.8(6.0)
-Males	25.9 (5.7)
-Females	28.9 (6.0)
Treatment of Diabetes:	
Proportions of patients (%)	
Oral hypoglycaemic agents (OHA)	74%
Insulin only	13%
Oral hypoglycaemic agents + Insulin	11%
Diet only	2%

Table 2

Laboratory findings of the study population

Mean (SD) Glycated Haemoglobin (HbAlc)%	8.5 (2.3)
Mean (SD) fasting blood glucose mmol/l	7.5 (3.9)
Mead (SD) of lipid profile in mmol/l	
Total Cholesterol	5.1 (1.0)
Low density Lipoprotein (LDL-C)	2.4 (0.9)
High Density Lipoprotein (HDL-C)	1.8 (0.5)
Triglycerides (TGs)	1.5 (0.8)
Proportion of patients with albuminuria	26%

Table 3

Quality of glycaemic control and proportion of patients in the study

HbAlc	Quality of control	Proportion of patients(%)
<8.0%	Ideal and Good	48
8.0-9.0	Fair/Intermediate	16
>9.0	Poor	36

A large proportion of 52% of the patients had HbAlc≥8% that is fair to poor glycaemic control.

Table 4

Magnitude of albumin excretion and proportion of patients with Albuminuria in the study

Lower range 20-<50mg	46%
Intermediate range ≥50-100mg	42%
Higher range >100mg	12%

Only one patient had macroalbuminuria with an accompanying very low creatine clearance of 4.7ml/min.

Only one out of seven patients in the study population had both retinopathy and albuminuria, the remaining six patients with retinopathy had no albuminuria. Amongst the patients who had albuminuria, 16 (61.5%) were males and 10 (38.5%) were females. There was a statistically significant (χ^2 P=0.043) association between male gender and presence of albuminuria, inspite of under-representation of males in the study population.

Table 5

Characteristics of patients with Albuminuria compared to Albuminuria-negative subjects in the study

		Albuminuria Positive n=26	Albuminuria Negative n=74	p-value
Mean (SD) age in years		52 (8.6)	54 (9.6)	NS
Mean (SD) HbAlc (%)		8.5 (2.3)	8.6 (2.3)	NS
Mean (SD) fasting glucose (mmol/l)		7.9 (5.0)	7.5 (3.7)	NS
	Mean (SD) TC	5.2 (0.7)	5.0 (1.1)	NS
Lipid	Mean (SD) LDL-C	2.5 (1.0)	2.4 (0.9)	NS
profile	Mean (SD) HDL-C	1.8 (0.5)	1.8 (0.5)	NS
	Mean (SD) TGs	1.7 (0.7)	1.5 (0.8)	NS
Mean (SD) creatine clearance ml/min/1.73m^2		96.9 (31.9)	93.1 (24.1)	NS
Mean (SD) of Blood	Systolic (mmHg)	143.0 (27.0)	136.2 (18.7)	NS
pressure	Diastolic (mmHg)	87.2 (16.2)	83.3 (13.1)	NS

NS= Difference not statistically significant

High blood pressure in patients was associated with lower mean (SD) of calculated creatinine clearance [84.7 (21.4)ml/min/1.73m^2] than that of patients with normal blood pressure which was 103.0 (26.9)ml/min/ 1.73m^2, a differenccce which was statistically significant (P=0.0005).

DISCUSSION

There was a female predominance of 67% in this study over males which may be a reflection of health-seeking behaviour amongst men and women in the clinic rather than prevalence. Most studies in this clinic show more females relative to the males. In the absence of a population survey, this number that favours females cannot be easily explained.

The causes of albuminuria in patients with type 2 diabetes mellitus are various and scantily investigated in this region, particularly in those patients without concomitant retinopathy.

Paving *et al.* (16) demonstrated in their prospective study the prevalence of non-diabetic kidney disease to be 25% in unselected consecutive patients with non-insulin independent diabetes mellitus with persistently elevated urinary albumin excretion ratio (UAER). Equally important in Parving's study was the 100% predictive value (of positive test) of retinopathy for diabetic glomerulopathy as the cause of albuminuria. Of the patients without diabetic retinopathy, 60% had diabetic glomerulopathy as cause of albuminuria. Our study has also revealed that above 90% of the patients with type 2 diabetes mellitus had albuminuria but without retinopathy by fundoscopy. Other cross-sectional studies(17-19) on nephropathy in type 2 diabetes mellitus have also found high prevalence of proteinuria but without retinopathy. It is therefore apparent that lack of retinopathy is a poor predictor of non-diabetic kidney disease in type 2 diaetes mellitus.

In our study, the traditional risk factors of hypertension, high HbAlc and dyslipidaemia were not significantly correlated with abuminuria. It is important to note that many (26%) patients in this study had albuminuria at this stage (mean duration 10 months) of type 2 diabetes. Prevalence of albuminuria in short-term type 2 diabetes has also been documented in several other studies: Keller *et al.*(20) found 14% had microalbuminuria, and 2% had macroalbuminuria. The Munich study(21) found 19% had microalbuminuria. and 5% had macroalbuminuria and UKPDS (22) found 17% had macroalbuminuria. The variation in prevalence of albuminuria in the various studies may be a reflection of methodological factors as well as differences in risk factors inherent in the populations under study. In our study we used a single morning urine specimen. A single untimed albumin measurement in urine for albuminuria has been used before and shown to have significant utility(23). When assessing the prevalence of macroalbuminuria in diabetes it is important to consider its prevalence in the background population. This information was lacking in our local background non-diabetic population. Asymptomatic diseases like hypertension and glomerulopathies in the absence of diabetes may account for albuminuria in some patients in the general population, some of which may later develop diabetes as a co-morbidity.

Arterial hypertension is prevalent in patients with type 2 diabetes with albuminuria(11,24). Hypertension enhances progression of diabetic nephropathy(25-27). There is consensus that arterial hypertension occurs more commonly in type 2 diabetes mellitus than in type 1 diabetes, even in prediabetic individuals(25-30). We also found hypertension to be quite prevalent at fifty four per cent in the study population. Fifty four per cent of these patients had it before the diagnosis of diabetes was made while in the remaining 46%, hypertension was diagnosed at examination. The role of "white coat" hypertension was not examined in this cross-sectional study. However, all patients categorised as hypetensive and were on treatment were not well controlled to appropriate targets. We did not ascertain the proportionate use of ACE-inhibitors, agents that may have mitigated presence and magnitude of albuminuria in the study subjects. The ACE inhibitor use, like other drugs, would be difficult to verify in our clinic because most patients purchase medications outside the hospital.

In this study, there was no statistically significant difference between blood pressures of patients with albuminuria and those without. However, the patients with hypertension had significantly ($p<0.00053$) lower creatinine clearance 84.7±21.4 ml/min than those without hypertension whose mean creatinine clearance was 103±26.9ml/min.

Male gender and older age onset, (above 40 years) have been found to be independent risk factors for nephropathy in type 2 diabetes mellitus(18,31). In this study, the mean (SD) of patients with albiminuria was 52 (8.6) years and the male patients were more at risk of having albuminuria iinspite of their under-representation in the study. There were more male smokers including current and ex-smokers in our study.

It was anticipated that the presence of albuminuria would be related to glycaemic control, like other. studies(20,32-34) have demonstrated. However, this was not our observation. While nephropathy in type 1 diabetes may exhibit a relatively predictable time-honoured process on exposure to chronic glycaemic excursions, this does not seem to be as predictable in type 2 diabetes., where complications may often be detectable at diagnosis(35). Our study addressed patients with type 2 diabetes of short duration and we did not do renal biopsies to exclude non-diabetic glomerulopathies.

Despite a significant proportion of patients with variable degrees of dyslipidaemia. there was also no

significant difference between the patients with and those without albuminuria. This observation was similar to that made by Keller *et al.*(20). However, treatment with pravastatin in a group of Japanese hypercholesterolaemic patients was noted to ameliorate albuminuria(36) suggesting a lipid-mediated role in nephropathy in that study population. This aspect needs further evaluation.

Type 2 diabetes mellitus is a polygeneic disease whose complications, just like its aetiology, may equally have a polygeneic background. The genes postulated to confer risk of developing (progressive) nephropathy are both haemodynamic and metabolic in roles. These include deletion allele of ACE gene(37) Sodium/Lithium (Na^+/Li^+) countertransporter(38). Genetic tests were not carried out in this study. Nonetheles, the implicit role played by as yet unknown multiple genetic factors may probably be important in these patients especially when the traditional risk factors developing diabetic nephropathy did dot attain levels of significance in this population who had a short duration of type 2 diabetes.

In summary, 26% of our patients who were recently diagnosed therefore had short-term type 2 diabetes already had albuminuria, a marker of nephropathy. More han 90% of these albuminuric patients did not have retinopathy (by clinical fundoscopic screening). The traditional risk (causative) factors of nephropathy like arterial hpertension, poor glycaemic control, smoking and dyslipidaemia did not exhibit a significant association with the presence of albuminuria at this early stage of type 2 diabetes in the study population. A significant proportion of our patients with short-term type 2 diabetes had already developed features of nephropathy. A longitudinal study with renal biopsies would be useful in this population to determine the proportionate role of non-diabetic causes of nephropathy within type 2 diabetis who have albuminuria. However, clinicians taking care of patients with type 2 diabetes should look for albuminuria because it is both a marker of nephropathy and cardiovascular risk factor(39) and aggressively address it in the way that would retard progression of renal dysfunction.

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