CONTROL OF RISK FACTORS FOR NEPHROPATHY AMONG NIGERIAN OUTPATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract
Background and Objectives: *To determine the proportion of type 2 diabetic outpatients with adequate control of risk factors for nephropathy in a Nigerian teaching hospital.*

Methods: *Between April and July 2005, 160 type 2 diabetic outpatients were assessed for control of average fasting blood glucose and blood pressure over 3 visits, and current use of ACE inhibitors. All patients were over 30 years of age and had been followed up for at least one year with at least 6 prior clinic visits.*

Results: *We studied 58 male and 102 female subjects with a mean (±SD) age of 54±10 years. The majority (54.7%) had diabetes between 1 and 5 years, and 95% were on antidiabetic drugs, most commonly both a sulphonylurea and metformin (64.5%). 114 (71.2%) were being treated for hypertension. The mean fasting blood glucose (FBS) was 7.6±2.9mmol/L, and 73 (45.6%) had good glycaemic control (mean FBS≤ 5.6mmol/L). A total of 51 (31.9%) had good blood pressure control (<140/90mmHg in non-hypertensives and <130/80mmHg in hypertensives), and 73 (45.6%) were currently receiving ACE inhibitors. Only five (3.1%) had the combination of good glycaemic control, good blood pressure control and received ACE inhibitors. Conversely, 23 (14.4%) had a combination of poor glycaemic control, poor blood pressure control, and were not receiving ACE inhibitors. Duration of diabetes ($p<0.01$), elevated creatinine ($p<0.01$), and elevated systolic blood pressure ($p<0.01$) were independently associated with proteinuria.*

Conclusion: *Despite the availability of measures to prevent the progression of diabetic nephropathy, control of risk factors was poor. Physicians and diabetic patients in Nigeria must work together to improve their management of risk factors for nephropathy.*
Key words: *Diabetes mellitus, chronic kidney disease, renoprotection*

INTRODUCTION

Diabetic nephropathy, a progressive complication of diabetes mellitus, is characterised by persistent albuminuria, elevated arterial blood pressure, and a relentless decline in glomerular filtration rate [1]. It is the leading cause of end-stage renal disease (ESRD) in Europe, Japan and the US, accounting for 25-30% of cases [2-4]. However, it is the third leading cause ESRD in Nigeria, accounting for up to 4% of patients with renal failure, behind hypertension and glomerulonephritis [5].

Multiple factors contribute to the initiation and progression of diabetic nephropathy [6]. Preventing or delaying progression is therefore an essential management goal. In many countries this goal remains elusive, despite clinically proven prevention strategies and guidelines [7]. The primary, potentially modifiable risk factors for diabetic nephropathy are sustained hyperglycaemia and hypertension. Other putative risk factors include glomerular hyperfiltration, smoking,

dyslipidaemia, proteinuria and dietary factors [2, 6, 8-10].

Clinical trials provide clear evidence that long-term targeted intensive interventions involving multiple risk factors retard the progression of diabetic nephropathy [3, 5, 9, 10]. Targets have been adopted by the World Health Organisation (WHO), International Diabetes Federation (IDF), and the American Diabetes Association (ADA) regarding control of risk factors for diabetic nephropathy [10-12], which include strict glycaemic control, control of hypertension, and early blockade of the renin-angiotensin-aldosterone system.

We were interested in finding out the use of nephropathy prevention strategies among type 2 diabetics attending the General Out Patients Department in a tertiary hospital in Nigeria.

Methods

Consecutive type 2 diabetic outpatients in the General Outpatient Department of the Jos University Teaching Hospital were recruited between April and July 2005. Eligible subjects were at least 30 years of age and had been followed for at least 6 months with at least 6 prior visits and complete medical records. Jos is an urban city located in the north central zone of Nigeria. Approval for the study was obtained from the Ethical Committee of the Jos University Teaching Hospital, and each subject provided written informed consent.

Each subject was interviewed using a standard questionnaire covering personal and disease history. Body weight and height were measured without shoes with patients in light clothing and the body mass index was calculated as the ratio of weight in kilograms to the height in metres squared (kg/m^2). Blood pressure was measured on the right arm using a mercury sphygmomanometer and appropriate cuff size with the subject seated for 5-10 minutes. Diastolic blood pressure was recorded as the phase V Korotkoff sound. The blood pressure readings of the preceding two visits were extracted from patient records and an average of the three readings used for analysis.

Each subject had a spot mid-stream urine tested for proteinuria (Medi-Test Combi 2; sensitivity of 10mg/dl). Fasting blood glucose (FBS) was estimated following an overnight fast by finger prick (capillary sample) using a standardised glucometer (LifeScan-Basic Plus-One Touch). Weekly calibration was performed according to the manufacturer's instructions. The last two FBS readings from the patient records were recorded, and the average of the three readings was used as an index of glycaemic control. Serum creatinine was estimated in the chemical pathology laboratory of the Jos University Teaching Hospital.

We used the ADA strategies and goals for reno- and cardioprotection in patients with diabetic nephropathy to define categories of desirable and undesirable glycaemic control and blood pressure [9]. Good glycaemic control was defined as mean FBS in the range of 3.6 – 6.7mmol/L, and poor glycaemic control as mean FBS>6.7mmol/L. Good blood pressure control was defined as systolic BP≤ 130mmHg and diastolic BP≤ 80mmHg in hypertensives or systolic BP<140mmHg and diastolic BP< 90mmHg in non-hypertensives. Poor blood pressure control was defined as values exceeding those limits.

An estimated sample size of 150 was calculated to allow a maximum 5% sampling error, and 160 subjects were recruited to allow for missing data. A p-value of 0.05 was considered significant. Data were entered, checked and analysed in Epi Info 3.2.2 (CDC, Atlanta, GA, USA). The chi-squared statistic and multiple logistic regression were used to test the association of patient characteristics with glycaemic control, blood pressure control, use of ACE inhibitors and proteinuria. Mean values of continuous variables were compared with the t-test.

Results

Patient characteristics

A total of 174 type 2 diabetic subjects were identified aged >30yrs at diagnosis and not insulin dependent. Five declined to participate, 7 were excluded due to incomplete past records, and two were too ill to participate, resulting in a total enrolment of 160. Their ages ranged from 32 to 85 years with a mean (±SD) age of 54±10 years. About 64% of subjects enrolled and studied were women as females tend to have better health seeking behaviour than men. Most (70.6%) had diabetes for 5 years or less, and only 11.9% had the disease more than 10 years (Table 1). Most subjects (71.2%) were being treated for hypertension, of which almost half (45.6%) received monotherapy. The most common antihypertensive agents used were ACE inhibitors (64%), followed by calcium channel blockers (54%) and thiazide diuretics (33%). Up to 5.6% of subjects had blood pressures in the hypertensive range but were undiagnosed and

not on treatment. The mean fasting blood glucose was 7.6±2.6 mmol/L, and 54.4% had poor glycaemic control.

Nephropathy prevention strategies

Figure 1 displays the overlap between the three nephropathy prevention strategies considered in this study. Only five subjects (3.1%) had all three prevention strategies implemented successfully. A total of 23 (14.4%) did not have adequate control of any of the three factors considered.

1. Glycemic control

Table 2 shows the relationship of patient characteristics with control of glycaemia and blood pressure. Increasing duration of diabetes was significantly related to poor glycaemic control (p for linear trend= 0.01). Subjects on non-pharmacologic therapy alone had significantly better glycaemic control than those on drug therapy (p= 0.02), although only 5% were not on drug therapy. Those on sulfonylurea monotherapy had significantly better glycaemic control and mean fasting blood glucose levels than those on other forms of therapy (p<0.01). Those using both insulin and oral hypoglycaemic agents had the worst glycaemic control and mean fasting blood glucose levels.

2. Control of hypertension

Hypertension was defined in subjects as a formal prior diagnosis of hypertension in their records on whatever treatment (lifestyle /drug). Those with no formal recorded diagnosis of hypertension were considered not to have hypertension, out of which those with SBP >140mmHg and or DBP >90mmHg were deemed to have undiagnosed hypertension.

A total of 51 (31.9%) had good blood pressure control (<140/90mmHg in non- hypertensives and <130/80mmHg in hypertensives). Increasing age was significantly related to an increasing mean systolic blood pressure (p= 0.04 for linear trend), but not to diastolic blood pressure (p=0.30) or overall blood pressure control (p=0.11).

3. ACE inhibitor use

Of all subjects, 46% were using ACE inhibitors, but only 14% had well-controlled blood pressure. Of hypertensives, 64% were getting ACE inhibitors but only 15% had well controlled blood pressure. ACE inhibitors were less likely to be used among those with good blood pressure control (OR 0.21, 95% CI 0.11-0.45). In analysis limited to hypertensive subjects, ACE inhibitor use was not associated with good blood pressure control (OR 1.28, 95% CI 0.37-6.3). Blood pressure control was not associated with gender, duration of diabetes, or BMI.

Proteinuria

Proteinuria was significantly more likely with increasing duration of diabetes (Table 3; p<0.01 for linear trend) and abnormal creatinine levels (OR 3.2, 95% CI 1.0-10.4). Mean systolic blood pressure was 150±25 mm Hg and 134±18 mm Hg in those with and without proteinuria, respectively (p<0.01). A total of 17 subjects with uncontrolled hypertension and 8 with proteinuria were not receiving ACE inhibitors. Serum creatinine levels were significantly higher in those with proteinuria (12043 mcmol/L) than in those without proteinuria (9531 mcmol/L; p<0.01). Use of ACE inhibitors was not associated with less likelihood of proteinuria (p=0.17). Duration of diabetes (p<0.01), elevated creatinine (p<0.01), and elevated systolic blood pressure (p<0.01) were independently associated with proteinuria in a multiple logistic regression
including all of these factors.

Discussion

This study provides evidence of poor control of risk factors for nephropathy in diabetic outpatients in north-central Nigeria. Studies focusing on management of diabetic nephropathy in nephropathy clinics have highlighted sub-optimal care, late referral, complexity of interventions, and the sheer size of the diabetic population as contributing to sub-optimal control of risk factors [11-16]. The gap between established treatment guidelines and their implementation is especially worrying in the light of the rapidly growing prevalence of diabetes [17]. Studies examining diabetes care in various clinical settings indicate that current practice is not achieving the goals for management of blood glucose, blood pressure, or serum lipids in individuals with diabetes [18]. The quality of care has been defined as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes are consistent with current professional knowledge”[19]. Even in high income countries only 11%, less than 80% and 56% of type 2 diabetics meet optimal levels for blood pressure control, haemoglobin A1c levels and angiotensin converting enzyme (ACE) inhibitor use, respectively [14, 20].
Despite the fact that all the diabetic subjects we

studied used some form of hypoglycaemic treatment, less than half of diabetic subjects in this study had good glycaemic control. In a U.S. general medicine clinic, 49% of patients on oral hypoglycaemic agents and 53% of African-Americans with type 2 diabetes on insulin had well-controlled glycaemia [16]. The third U.S. National Health and Nutritional Examination Survey (NHANES III) and the Behavioural Risk Factors Surveillance System (BRFSS) recorded good glycaemic control (HbA1c<9.5%) in 75% of subjects, but only 43% had HbA1c values below 7% [14]. In the more recent NHANES IV, only 37% had HbA1c values below 7% [18]. However, direct comparison with these studies is limited, because we used average fasting blood glucose values rather than HbA1c as an index of glycaemic control. A mean fasting blood glucose <6.7mmol/L correlates well with a normal haemoglobin A1c level between 4-6% [21].

In this study, glycaemic control worsened with increasing duration of disease. This likely resulted from a decline in β-cell function with increasing duration of diabetes. Good glycaemic control was associated with sulfonylurea monotherapy and poor control with combined insulin and oral hypoglycaemic therapy, suggesting that the more severe the diabetes, the more difficult it is to control. Physicians may exercise excessive caution in prescribing multiple agents and insulin in order to avoid hypoglycaemia. Adherence is more difficult with multiple drugs, particularly in developing countries, because of increased cost, insulin storage requirements, infrequent use of self blood-glucose monitoring, and limited patient education personnel and resources.

Although 71% of diabetic patients were being treated for hypertension, only 9% had well controlled blood pressures (<130/80 mm Hg). In south-western Nigeria, only 11% of type 2 diabetics on treatment for hypertension had blood pressures below 140/90 mm Hg [22]. Studies in Bahrain and Italy showed similar proportions of patients attaining target blood pressure levels of 11% and 13%, respectively [23, 24]. In NHANES IV, 36% of diabetic subjects achieved target blood pressures below 130/80 mm Hg [18]. Blood pressure control may be more difficult to achieve in black Africans than in predominantly white populations. The cost of continuous antihypertensive use is borne directly by patients in our setting, resulting in erratic adherence for a largely asymptomatic condition. We did not measure adherence to therapy, nor did we consider the many factors that influence adherence.

Encouragingly, we found that ACE inhibitors were the most frequently prescribed antihypertensive agents (64%). In another Nigeria centre, only 11.3% of hypertensive diabetics were prescribed ACE inhibitors [22]. An American analysis showed that use of RAAS blockade increased by 50% and 37% in two locations from 1997 to 2001 [25]. In another study 55% of diabetic patients were using RAAS blockade, of whom 39% had well controlled blood pressure [13]. Interestingly, more type 2 diabetics in our study received ACE inhibitors than had good glycaemic control or optimal blood pressure control. The low proportion with controlled blood pressure among our subjects using ACE inhibitors further buttresses the need for frequent review, dosage adjustment, and multiple antihypertensive agents to meet blood pressure targets. We did not evaluate the indications and contraindications to ACE inhibitors in individual subjects. This information would potentially have been useful in determining if the use of such drugs was below target levels. We did not test for microalbuminuria as an indication for RAAS blockade, as this investigation is not routinely available in Nigeria.

In terms of nephropathy prevention strategies, a total of 45% had adequate glycaemic control, 32% had optimal blood pressure control, and 46% were receiving ACE inhibitors. However only 3% of all subjects simultaneously had good glycaemic control, optimal blood pressure, and were receiving ACE inhibitors. These three cardinal targets, each independently capable of preventing the development of nephropathy, have a summative effect when used together. Multifactorial interventions are advocated for the prevention of chronic complications of diabetes, like nephropathy [10, 26].

Most of our subjects that had diabetes for 5 years or less, representing an ideal time for intervention to forestall future complications. However, in many resource-poor countries, guidelines are difficult to implement because of drug costs and limited resources. More studies are needed to assess the factors that contribute to non-adherence and failure to achieve set targets in developing country settings.

Table 1: Characteristics of 160 Nigerians with Type 2 Diabetes

Characteristic	No. (%)
Sex	
Female	102 (63.7)
Male	58 (36.3)
Duration of Diabetes	
<1 yr	27 (16.9)
1-5 yrs	86 (53.8)
6-10 yrs	28 (17.5)
11-15 yrs	11 (6.9)
>15 yrs	8 (5.0)
Type of Therapy	
Drug Therapy	152 (95)
Diet Alone	8 (5)
Antidiabetic Drugs	
Sulfonylurea	22 (14.5)
Biguanide	16 (10.5)
Biguanide & Sulfonylurea	98 (64.5)
Insulin & Oral Hypoglycaemic	16 (10.5)
Antihypertensive Therapy	
Yes	114 (71.2)
No	46 (28.8)
ACE Inhibitor Therapy	
Yes	73 (45.6)
No	87 (54.4)
Obesity Class (BMI kg/m^2)	
Underweight (<18.5)	1 (0.6)
Normal (18.5-25)	41 (25.6)
Overweight (25.1-29.9)	72 (45)
Obese (=30)	46 (28.8)
Glycaemic control (FBS mmol/L)	
Good (3.6- 6.7)	73 (45.6)
Poor (> 6.7)	87 (54.4)
Blood Pressure	
Normal	37 (23.1)
Controlled	14 (8.8)
Uncontrolled	100 (62.5)
Untreated	9 (5.6)
Proteinuria	
Yes	20 (12.5)
No	140 (87.5)
Abnormal Creatinine(µmol/L)	
Yes (>126)	18 (11.3)
No (=126)	142 (88.7)

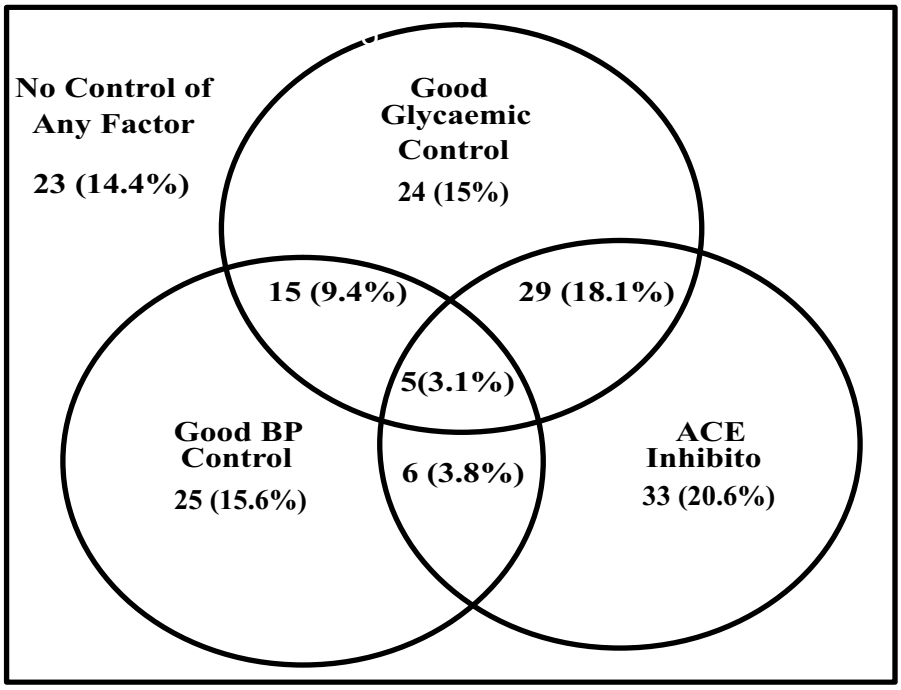
Table 2: Characteristics associated with Glycaemic and Blood Pressure Control

Characteristic	Good glycaemic control		P value	Good blood pressure control		P value
	Yes N=73	No N=87		Yes N=51	No N=109	
Duration of Diabetes						
<1 yr	15 (55.6)	12 (44.4)		9 (33.3)	18 (66.7)	
1-5 yrs	43 (50)	43 (50)		24 (27.9)	62 (72.1)	
6-10 yrs	11 (39.3)	17 (60.7)		10 (35.7)	18 (64.3)	
11-15 yrs	3 (27.3)	8 (72.7)		4 (36.4)	7 (63.6)	
>15 yrs	1 (12.5)	7 (87.5)		4 (50)	4 (50)	
Antidiabetic Drugs			<0.01			
Sulfonylurea	17 (77.3)	5 (22.7)				
Biguanide	10 (62.7)	6 (37.5)				
Biguanide & Sulfonylurea	36 (36.7)	62 (63.3)				
Insulin & Oral Hypoglycaemic	3 (18.8)	13 (81.2)				
Antihypertensive Therapy						<0.01
Yes				16 (14.0)	98 (86.0)	
No				35 (76.1)	11 (23.9)	
ACE Inhibitor Therapy						<0.01
Yes				11 (15.1)	62 (84.9)	
No				40 (46.0)	47 (54.0)	
Obesity Class (BMI kg/m^2)			0.19*			0.33*
Underweight (<18.5)	0 (0)	1 (100)		1 (100)	0 (0.0)	
Normal (18.5-25)	14 (34.1)	27 (65.9)		15 (36.6)	26 (63.4)	
Overweight (25.1-29.9)	37 (51.4)	35 (48.6)		22 (30.6)	50 (69.4)	
Obese (=30)	22 (47.8)	24 (52.2)		13 (28.3)	33 (71.7)	

Table 3: Proteinuria and Risk Factors

Characteristic	Proteinuria		P value
	Yes N=20	No N=140	
Duration of Diabetes			<0.01*
<1 yr	1 (3.7)	26 (96.3)	
1-5 yrs	10 (11.6)	76 (88.4)	
6-10 yrs	3 (10.7)	25 (89.3)	
11-15 yrs	2 (18.2)	9 (81.8)	
>15 yrs	4 (50)	4 (50)	
Antihypertensive Therapy			0.51
Yes	16 (14.0)	98 (86.0)	
No	4 (8.7)	42 (91.3)	
ACE Inhibitor Therapy			0.17
Yes	12 (16.4)	61 (83.6)	
No	8 (9.2)	79 (90.8)	
Glycaemic control (FBS mmol/L)			0.13
Good (3.6 - 6.7)	6 (8.2)	67 (91.8)	
Poor (> 6.7)	14 (16.1)	73 (83.9)	
Abnormal Creatinine(µmol/L)			0.04
Yes (>126)	5 (27.8)	13 (72.2)	
No (=126)	15 (10.6)	127 (89.4)	

Figure 1: Proportions of 160 Nigerian Diabetics Achieving Three Nephropathy Prevention Strategies.



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