MORBIDITY IN RELATION TO STAGE OF DIABETIC NEPHROPATHY IN TYPE-2 DIABETIC PATIENTS

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Aims of the study: Type-2 diabetic patients have excessive cardiovascular mortality, primarily related to diabetic nephropathy. The extent of the morbidity due to nephropathy in type-2 diabetes mellitus has not been fully quantified in Nigeria. This study aims to quantify the prevalence of micro- and macrovascular complications in hospitalized type-2 diabetic patients with nephropathy.

Methods: Over a three-year period, 465 type-2 diabetic patients were examined for nephropathy and diabetic associated diseases while on hospital admission.

Results: One-hundred-ninety-one patients (41.1%) had signs of different stages of diabetic nephropathy. There is a predominance of the male sex in the nephropathic groups. Disease duration is lowest in the non-nephropathic group (6.5±7.1years) but varies between 9.4±4.1 years and 11.7±3.5 years in the nephropathic groups. Hypertension, left ventricular hypertrophy, stroke, and myocardial infarction were less common in the non-nephropathic group, $p<0.05$, but showed an upward trend with progression of nephropathy. Although foot amputation was uncommon, the total percentage of patients with diabetic foot increased with progression of nephropathy (17% in non-nephropathic group versus 67% in patients with chronic renal insufficiency). The overall prevalence of diabetic retinopathy increased with progression of nephropathy, especially the occurrence of proliferative retinopathy.

Conclusions: A high morbidity was already present even in patients without nephropathy that increased in the course of the development of nephropathy. The study identifies patients with diabetic nephropathy as a high-risk group for excess cardiovascular morbidity in Nigeria. Thus, it is imperative to aggressively prevent or slow down progression of diabetic nephropathy. (*J Natl Med Assoc.* 2003;95:1042-1047.)

Key words: type-2 diabetes ♦ morbidity ♦ diabetic nephropathy ♦ Nigeria

INTRODUCTION

Type-2 diabetes mellitus is characterized by disorders of insulin action and insulin secretion, either, of which may be the predominant feature[1]. It is the *most* common form of diabetes mellitus and is almost always associated with insulin resistance.

Generally, the population of patients with type-2 diabetes mellitus is at least 10 times more than the population with type-1 diabetes mellitus[2]. In the United States, the prevalence of diabetes mellitus is 3.1% of which over 90% is of type-2 diabetes mellitus[3]. Furthermore, the incidence of diabetic nephropathy (DN) has increased by 150% in the past 10 years, a trend also seen in Europe[4,5]. Generally in the western countries and Japan, diabetes mellitus is the single most important disorder

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Table 1. Clinical Characteristics of Type-2 Diabetics According to Stage of Nephropathy

	Stage ≤III	Stage IV	Stage Va	Stage Vb
Number of patients	107	54	21	9
Age (years)	52±5.8	53.4±6.3	55.2±4.9	53±3.3
Duration of diabetes (years)	6.5±7.1	9.4±4.1	11.2±3.2	11.7±3.5
Sex distribution (M:F)	1:1.4	1.2:1	1.6:1	1.4:1
Body mass index (Kg/m^2)	28	26.8	24.8	23.4
Admission BP: Systolic/diastolic (mmHg)	138/90±25/15	160/95±30/15	170/100±30/15	170/110±40/20
Discharge BP: Systolic/diastolic (mmHg)	120/70±10/5	140/80±15/10	150/95±16/9	145/90±10/5
Hypertension (%)	55	79.2	75	87
LV hypertrophy (%)	33	73	72	77
Stroke (%)	16	25	33	27
Myocardial infarction (%)	0	1	3	2
Peripheral vascular disease (%)	33	45	58	72
Neuropathic ulcer (%)	14	19	22	34
Neuroischemic ulcer (%)	3	8	13	33
Total with foot lesion	17	27	35	67
Amputation (%)	0	1	2	1
Retinopathy				
Background (%)	28	45	42	38
Proliferative (%)	7	16	22	36
Total % with retinopathy (%)	35	61	64	74
Blindness (%)	0	1	1	0
Cataract (%)	18	22	24	18
Drug therapy				
OHA (%)	56	48	46	28
Insulin (%)	26	28	12	18
OHA and insulin (%)	4	-	-	-
Diet alone (%)	14	24	42	54

Staging ≤III: with or without microalbuminuria
IV: Clinical diabetic nephropathy
Va: Renal insufficiency
Vb: Requires dialytic therapy
OHA: Oral hypoglycemic agents

leading to renal failure in adults accounting for more than 25% of all end-stage renal disease[6]. In Nigeria, the national prevalence of diabetes mellitus is 2.2%[7] with a progressive rise in the incidence of DN from 19% in 1971[8] to 28.4% in 2003[9]. Diabetes mellitus is the third most common cause, after glomerulonephritis and hypertension, of chronic renal disease in Nigerians[10].

Micro- and macrovascular complications are particularly frequent in patients who have type-2 diabetes mellitus[11]; these patients have excessive cardiovascular mortality[12]. About 40% of type-2 diabetic patients develop DN in the course of their disease[13]. Mongensen et al.[14] identified five stages of progression in the natural history of DN: renal hypertrophy and hyperfunction phase, silent phase, incipient DN, overt DN and end-stage renal failure. The blood pressure is normal in the first three stages but begins to rise in stage 4. The first sign of renal involvement in patients with type-2 diabetes is most often microalbuminuria, which is classified as incipient nephropathy[15]. Progression to macroal-

buminuria or overt nephropathy occurs in 20–40% of patients. In untreated patients, the glomerular filtration rate falls at an average of 10–12 ml per minute per year[16,17]. It is frequently accompanied or followed by the appearance of hypertension and deteriorating kidney function[9,17].

In Nigeria, the extent of the morbidity due to nephropathy in type-2 diabetes mellitus has not been fully quantified. Therefore, a prospective study on the prevalence of micro- and macrovascular complications was conducted in hospitalized type-2 diabetic patients.

PATIENTS AND METHODS

The study group consists of consecutive type-2 diabetic patients admitted to the wards of the Olabisi Onabanjo State University Teaching Hospital, Sagamu, Ogun State, Nigeria, for diabetes-related causes, including blood sugar and blood pressure control, nephrological evaluation, and atherosclerotic complications. The hospital is comprised of 185 beds: 40 medical beds, 51 pediatric beds, 61 surgical beds, and 33 obstetrics/gynecological beds, (excluding the accident and emergency unit, which serves as a rapid transit unit for patients). In the hospital, type-2 diabetes patients were hospitalized usually under any of the general internal medicine subspecialties, including endocrinology and nephrology with an attendant dialysis unit. Sagamu's and its environs' population of about 2.5 million is also served by several other hospitals, including three tertiary and four privately owned hospitals with dialysis facilities in the neighboring states of the federation.

Type-2 diabetic patients are those diabetics on oral hypoglycemic agents (OHA). Diabetics on OHAs but who required insulin during an acute illness were classified as type-2. Those whose diabetic state has been controlled on diet but previously on oral hypoglycemic agents were also classified as type 2. Patients with onset of diabetes after the age of 40 years and a body mass index (BMI) above normal ($\geq$25 kg/m^2 in females and $\geq$27 kg/m^2 in males) were taken as type-2 diabetic patients.

Clinical parameters, including current age, sex and duration of diabetes mellitus, drug therapy, clinical symptoms, BMI, and blood pressure, were recorded. Blood pressure was measured twice during the study (on admission and before discharge) and was recorded to the nearest 2 mmHg. A cuff size of 20–31 cm was used in patients with an upper-arm circumference less than 32 cm, and a cuff size of 28–36 cm was used in patients with an upper arm circumference above 32 cm. Systolic and diastolic blood pressures were taken as the appearance and disappearance of the Korotkoff sounds (phases I and V respectively). Hypertension was defined as systolic blood pressure of $\geq$140 mmHg and/or diastolic blood pressure of $\geq$90 mmHg. Patients already on antihypertensives were taken as hypertensive.

The occurrence of myocardial infarction and stroke was taken from clinical history and previous documents or as an acute event. Peripheral vascular disease was defined as an ankle to brachial-systolic pressure ratio of less than 0.9 in either leg. The earliest sign of neuropathy was examined for by vibration testing with a 128 Hz tuning fork. Ulcers were defined according to medical history, ankle blood pressure, and sensory examination. Ulcers in patients with prevalent neuropathy and typical location on pressure points were defined as neuropathic ulcers, whereas ulcers associated with ankle pressure below 50 mmHg were defined as neuroischemic ulcers because of the usual coexistence of ischemia and neuropathy. Amputations were recorded. Diagnosis of the ophthalmologic status was made and classified into background retinopathy, proliferative retinopathy, cataract, and blindness.

Laboratory parameters to assess renal function, fasting cholesterol and triglycerides, fasting and two-hour postprandial blood sugars, and the packed cell volume, were estimated. Urinalysis and urine microscopy, 24-hour urinary protein and creatinine clearance were done. Completeness of 24-hour urine collections was assessed by direct questioning and urinary creatinine. Left ventricular hypertrophy was diagnosed using the Araoye criteria for Negroes[18], which has been validated as the best option for Nigerians.

Staging of nephropathy was done according to dipstick findings (after treatment of *any* urinary infection), presence of proteinuria, hypertension and creatinine clearance results[14].

Quantitative data was expressed as mean ± S.D. Student's t/chi-square tests were used to assess the difference among the various subject groups. Correlation was by the Spearman correlation coefficient, and significance was taken at $p<0.05$.

RESULTS

Between September 1999 and August 2002, 465 type-2 diabetic patients were examined for nephro-

Table 2. Laboratory Data of Type-2 Diabetics According to Stage of Nephropathy

	Stage ≤III	Stage IV	Stage Va	Stage Vb
Fasting blood sugar (mmol/l)	6.2±0.6	6.7±0.6	6.6±0.6	6.4±0.6
Two-hour postprandial blood sugar (mmol/l)	10.8±0.6	10.5±0.6	9.8±0.6	10.4±0.6
Cholesterol (mg/dl)	239±82	258±66	277±52	265±49
Triglyceride (mg/dl)	198±55	210±115	288±98	245±112
Creatinine (mg/dl)	0.8±0.3	1.2±0.25	2.6±1.44	6.4±3.6
Proteinuria (g/dl)	0.2±0.44	1.6±0.36	2.6±0.64	–

Staging <III: With or without microalbuminuria
IV: Clinical diabetic nephropathy
Va: Renal insufficiency
Vb: Requires dialytic therapy

pathy and diabetes, associated diseases during hospital admission treatment period. One-hundred-ninety-one patients (41.1%) had signs of different stages of DN. Tables 1 and 2 show the clinical characteristics and laboratory data of the study group according to stage of nephropathy, respectively.

The mean age is similar in all groups with predominance of the male sex in the nephropathic groups (stages IV and V). The duration of disease is lowest in the non-nephropathic group (6.5±7.1years); it varies between 9.4±4.1 years and 11.7±3.5 years in the nephropathic groups. Sole therapy with diet alone increased through the different stages of nephropathy. The combination therapy of insulin with an oral agent was uncommon (4% in the non-nephropathic group and none in the nephropathic group). With progression of nephropathy, there was a progressive reduction in the BMI. Patients with clinical nephropathy and renal insufficiency were slightly underweight.

The mean admission blood pressure of 138/90 mmHg was significantly lower among the non-nephropathic group, compared to the nephropathic groups (stage IV—160/95 mmHg, Va-170/100 mmHg and Vb-170/110 mmHg), $p<0.05$. An upward trend in the admission blood pressure was observed from the non-nephropathic group through to the dialytic group, $p<0.05$. Blood pressures on discharge were better among the non-nephropathic group and in patients with stage-IV DN than in patients with stage-V DN. Hypertension, left ventricular hypertrophy, stroke, and myocardial infarction were less common in the non-nephropathic group, $p<0.05$. They showed an upward trend with progression of nephropathy.

Although limb amputation was uncommon within the population and most ulcers were neuropathic, the total percentage of patients with diabetic foot increases with progression of nephropathy (17% in non-nephropathic group versus 67% in stage Vb).

The overall frequency of occurrence of diabetic retinopathy increased with progression of nephropathy, especially the occurrence of proliferative retinopathy. Background diabetic retinopathy was more common in the nephropathic group. Very few of the patients were blind, while the occurrence of cataract did not follow any pattern with progression of nephropathy.

Table 2 showed that the mean fasting blood sugar and the two-hour postprandial was similar in all groups. Although the absolute lipid levels were lower in the non-nephropathic group compared to the nephropathic group, there was no significant difference in lipid levels with progression of nephropathy, $p>0.05$. Expectedly, there was a progressive increase in the serum creatinine and the degree of proteinuria with progression of nephropathy.

DISCUSSION

This study shows a male preponderance in the nephropathic group. The role played by the male sex hormones in promoting DN has been documented[19].

The mean duration of disease is longer than previous studies in the same environment[20,21]. The increased mean duration of disease recorded may be due to increased longevity, awareness, and better management of diabetic state when compared to the situation in the early 1960s (Thomas[20] recorded a mean of 3.9 years; and Greenwood and Taylor[21], a mean of 4.2 years among the same tribe).

Significantly, the mean duration of disease differ between the non-nephropathic and the nephropathic group (<10 years and >10 years, respectively).

Generally, type-2 diabetic patients have excessive cardiovascular mortality; the excess mortality is primarily related to DN[12]. Previously, the extent of the morbidity due to DN had not been quantified in Nigeria. This study demonstrated that the well-known cardiovascular risks of systemic hypertension, left ventricular hypertrophy and stoke, and diabetic complications such as diabetic retinopathy and peripheral vascular disease occur more commonly with progression of DN among type-2 Nigerian diabetic patients. The higher cardiovascular morbidity with progression of nephropathy could explain why these patients die before progressing to end stage renal failure[22]. A similar finding of high morbidity of type-2 patients on dialysis has been reported among caucasians[22] and Pima Indians[23]. The pathogenesis of the increasing stages of nephropathy has been recently summarized[24]. This include accumulation of advanced glycation end products with renal disease, a pathogenic modification of LDL cholesterol by advanced glycation end products, an increase in sialic acid in nephropathy and a generalized vasculopathy with a reduced content of heparansulfate in renal and vascular basal membranes[24]. Others are the aldose reductase (polyol formation) pathway, de novo synthesis of diacylglycerol, nonenzymatic glycation, glucose antioxidation and dicarbonyl or lipid peroxidative stress[24]. Vascular damage by hypertension is also excercabated in DN[24].

The combination therapy of insulin with an oral agent was rarely prescribed in the hospital. It is known that more than 50% of patients with type-2 diabetes mellitus will require insulin treatment as a result of progressive pancreatic beta-cell failure[25]. Generally, the combination therapy of insulin with an oral agent improves glycemic control in type-2 diabetic patients[26]. The Diabetes Control and Complications Trial[27] has demonstrated that intensive diabetes treatment delays the onset (by 34%) and slows the progression of nephropathy (by 56%). Considering also the beneficial effect of metformin on insulin resistance, it is recommended that metformin-insulin treatment regimen should be encouraged to achieve intense blood glucose control with a view to preventing or delaying the onset of DN.

Generally, strategies to reduce progression in renal diseases have recently been elucidated[28]. The progression promoters of DN have been identified to be hypertension, proteinuria, lipid abnormalities, and hyperglycemia[28]. Strict control of these factors should be encouraged so as to slow progression of DN and the associated comorbidity in this population.

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