Original Article

Review of Diabetic Nephropathy Naive Patients in Endocrinology Clinic: A Teaching Hospital Experience

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Abstract

Background: Diabetes mellitus has continued to be a worrisome public health challenge with global prevalence estimated at 6.4% population of about 300 million in 2010. Local studies in Nigeria have submitted prevalence ranging between 3 to 5.7%. Diabetic nephropathy or diabetic kidney disease is a progressive microvascular complication of diabetes mellitus characterized by increased hyper-albuminuria and or progressive deterioration in glomerular filtration rate. The highest global prevalence of developing chronic kidney disease from DM was documented in Asia at an average of 36% while Africa reported a range from 2 to 41%. **Methodology**: This was a hospital- based cross-sectional, observational retrospective of 251 patients that attended the clinic of the university from February 2020 to February 2021. Consent for the study was obtained from the university management. The inclusion criteria comprised all subjects diagnosed with diabetes and on treatments, presence of positive urine protein albustix repeated at two to four weeks interval with no other clinical or laboratory evidence of kidney diseases. Data were retrieved and analyzed with SPSS 23.0. **Result:** A total number of 251 subjects who attended the university clinic were enlisted in this study. The average age was 52.6±13.1. There were more females 144(57.4%) than males 107(42.6%). The mean duration of diabetes was 10±5.5yrs. The average BMI was 27.9±5.8 (kg/m^2). The mean fasting blood sugar was 9.7 += 4.0 mmol/l. The prevalence of diabetic nephropathy as indicated by proteinuria was 8.4%. There was a significant association between elevated HBAIC, proteinuria and serum creatinine with (P≤0.05). Logistic regression results showed that subjects with FBS ≥ 7.0 mmol/l were 14 times more likely to develop proteinuria with confidence intervals at 95% (11.688-108.263). **Conclusion:** This study revealed that 8.4% of the patients were diabetic nephropathy naive and majority of the subjects were captured in stage 3 CKD. The study also showed significant association between poor glycaemic control, anaemia and serum creatinine. This group of patients requires close monitoring and follow up in the clinic to prevent regression of renal functions.

Key words: Proteinuria, Diabetic mellitus, Creatinine, Chronic kidney disease

INTRODUCTION

Diabetes mellitus has continued to be a worrisome public health challenge with global prevalence estimated at 6.4% at a population of about 300 million in 2010. Diabetes mellitus is estimated to rise exponentially to half a billion population by the year

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2030. Local studies in Nigeria have submitted prevalence ranging between 3 to 5.7%. In meta-analysis, the aggregate prevalence of DM among Nigeria adults was 5.77%[1,2]

The burden of the disease is alarming. It accounts for about 22% of deaths in Nigeria [2,28, The] complications are multi-systemic and can be caused majorly by both Type 1 and Type 2 DM. Studies have shown that Type 2 DM accounts for about 90% of DM complications, of which diabetic nephropathy is the most fatal with its attendant resultant end stage renal disease[3]

Diabetic nephropathy or diabetic kidney disease is a progressive microvascular complication of diabetes mellitus characterized by increased hyper albuminuria and or progressive deterioration in glomerular filtration rate. The highest global prevalence of developing chronic kidney disease from DM was documented in Asia with 38.8% in China and 34.4% in India respectively in a cross-sectional study from a risk assessment management program, while local studies in Nigeria and Africa have submitted lower prevalence averaging 22% of diabetic nephropathy comparatively [4, 5] Diabetic nephropathy accounts for 30% of the cause of end stage renal disease globally after hypertension and chronic glomerulonephritis[6].

The injurious effect of long standing poorly controlled hyperglycemia results in macrovascular complications (coronary artery disease, peripheral arterial disease stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy). These Complications can involve multiple systems that are susceptible to the detrimental effects of oxidative stress and apoptotic cell injury [7]

The prevalence of diabetes around the world has reached epidemic proportions, with estimations suggesting that more than 40% of people with diabetes will develop chronic kidney disease (CKD), including a significant number who will develop end stage kidney disease (ESKD) requiring renal replacement therapies [8] Diabetic nephropathy is a third leading cause of end-stage renal failure accounting for 35% to 40% of all new cases requiring dialysis therapy throughout the world [8,28]. The incidence of diabetic kidney disease in Africa, especially in Nigeria is underreported but there has been a concomitant rapid increase in the incidence of diabetic nephropathy. A progressive rise in the incidence of diabetic nephropathy in Nigeria was from 19% in 1971 to 28.4% in 2003 as well as its equal burden of end-stage renal disease [9]

Early diagnosis of diabetic nephropathy is characterized by evidence of microalbuminuria or bed side dipstick proteinuria. The global prevalence of microalbuminuria in diabetes mellitus is 39%[10]. Other significant pathognomonic abnormalities include a progressive reduction in glomerular filtration rate, hypertension and anaemia. Other risk factors inherent in diabetic kidney disease include obesity, increased genetic predisposition, renal renin-angiotensin-aldosterone system (RAAS) and lipid disorders [11, 12] Treatment focus for diabetic patients arriving in the clinic has usually been on glycemic control, and control of blood pressure levels, whereas some patients upon screening already present with symptoms accompanying diabetic complications. For the purpose of achieving better treatment targeted at specific complications that may pose to claim the lives of these patients, such patients rather than being retained in the diabetic clinic should be referred to the special units handling respective complications in order to decrease the progression of such complications were established with further informed treatment efforts. Early diagnosis of diabetic nephropathy and appropriate interventions offer therapeutic advantages in controlling the progression of the disease and therefore increasing life expectancy. This study aimed to examine the percentage of diabetic patients between the years February 2020 to February 2021 with or without presenting symptoms of diabetic nephropathy at the diabetes clinic of the university.

METHODOLOGY

This was a hospital-based cross sectional retrospective observational p study of 251 subjects who attended the endocrinology clinic seen from February 2020 to February 2021. The ethical approval for the study was obtained from the Health Research Ethic Committee (HREC) of the institution. The inclusion criteria comprised all subjects diagnosed with diabetes mellitus on treatments, with documented evidence of presence of two positive albustix or persistent proteinuria (proteinuria that was documented twice within 2 to 4 weeks) [21, 22], presence of diabetic retinopathy with no clinical or laboratory evidence of any kidney diseases or renal tract diseases. Renal function indices were indicated by documented evidence of electrolyte urea and creatinine. Abnormal serum creatinine was taken as equal to or greater than 1.3mg/dl or 115mmol/l and the modified diet in renal diseases (MDRD) formular was used to estimate glomerular filtration rate (GFR). (MDRD has been

well validated in patients with various degree of renal impairment except those in end-stage), Subjects' haematocrits were obtained to assess the degree of anaemia. The folders were retrieved by simple random sampling method and relevant information documented in Excel. Data were retrieved from the records of patients' folders that met the inclusion criteria. Data were analyzed using SPSS 23.0. The analysis included frequency distribution, means, percentages with suitable tables and graphs. The Chii square test was used to determine association between variables. $P < 0.05$ was taken as significant statistically.

RESULTS

A total number of 251 subjects attending diabetic clinic at the university teaching hospital were used to perform this study. One hundred and forty-seven (58.6%) of the subjects were in the age group of 50-69 years. One (0.4%) was above 90 years. The average age was 52.6±13.1 with a range of 13-90 years old. The mean weight of the subject was 76.7± 17.3kg with a range of 30 to 120kg. The average height of the subjects was 1.65± 0.8m with a range of 1.36 – 1.86m.

Table 1: Demographic Characteristics of Subjects

Variable	Frequency N= 251	Percentage (%)
Age Group		
10 to 29	7	2.8
30 to 49	58	23.1
50 to 69	147	58.6
70 to 89	38	15.1
≥ 90	1	0.4
Age range	**13 - 90**	
Mean ± SD	**56.2 ± 13.1**	
Gender		
Male	107	42.6
Female	144	57.4
Duration of Diabetes(years)		
1 to 5	87	34.7
6 to 10	75	29.9
11 to 15	42	16.8
16 to 20	47	18.7
Age range	**1.5 - 19**	
Mean ± SD	**10 ± 5.5**	

There were more females 144(57.4%) than males 107(42.6%) The mean duration of diabetes of the subjects was 10±5.5yrs with a range of 1.5 to 19 years**.**

The average BMI was 27.9±5.8 (kg/m^2) with a range of 13-90 (kg/m^2). The mean fasting blood sugar level of the subject was 173.9± 72.4(mg/dl) with a range of 72 to 514(mg/dl). The average HBA1C of the subjects was 8.7± 2.9 % with a range of 4.3 – 28.1% and the average PCV of the subjects was 35.6± 6.1 % with a range of 20 – 53.4%

Table 11: Laboratory Test Result of The Subjects

Variable	Frequency (N=251)	Percentage (%)
BMI		
<18.5	10	4.0
18.5 to 24.9	71	28.3
25 to 29.9	91	36.3
≥ 30	79	31.5
Mean ± SD	**27.9±5.8**	
Range	**15 - 43**	
FBS(Mg/dl)		
70 to 110	41	16.3
111 to 125	37	14.7
≥ 126	173	68.9
Mean ± SD	**173.9±72.4**	
Range	**72 - 514**	
HBA1C (%)		
≤ 6.5	86	34.3
> 6.5	165	65.7
Mean ± SD	**8.7± 2.9**	
Range	**4.3 – 28.1**	
PCV (%)		
Anemia	53	21.1
Normal	198	78.9
Mean ± SD	**35.6± 6.1**	
Range	**20 – 53.4**	

Table 111: Kidney function Parameters of the subjects

Variable	Frequency (N=251)	Percentage (%)
Creatinine(mg/dl)		
< 1.3	221	88.0
≥ 1.3	30	12.0
Mean ± SD	**1± 0.4**	
Range	**0.42 – 5.3**	
eGFR (ml/min/1.73m^2)		
≥ 90	130	51.8
60 to 89	94	37.5
45 to 59	18	7.2
30 to 44	8	3.2
15 to 29	1	0.4
<15	0	0.0
Mean ± SD	**91.7± 33.0**	
Range	**26 – 225**	
Protein		
Positive	21	8.4
Negative	230	91.6
Cast		
Positive	9	3.6
Negative	242	96.4

The average serum creatinine level was 1.0±0.4 (mg/dl) with a range of 0-42(mg/dl) The mean estimated glomerular filtration rate of the subject was 91.7± 33.0(ml/min/1.73m^2**)** with a range of 26 to 255 **(**ml/min/1.73m^2**).** Twenty-one (8.4%) of the subjects had protein in the urine**.**

The prevalence of diabetic nephropathy as indicated by proteinuria (8.4%), PCV (21.1%) and serum creatinine (12%).

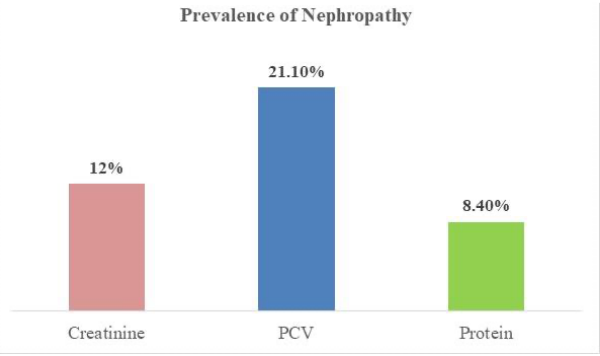

Fig 1: Determinant of diabetic nephropathy by Creatinine, proteinuria and PCV

Table 1V: Association between, PVC, HBA1C, FBS, BMI and eGFR

Variable	eGFR (Freq (%) (n=224) - <60(n=27)		X^2	Df	P-Value
PCV (%)					
Anemic	39(73.6)	14(26.4)	17.159	1	0.001*
Normal	185(93.4)	13(6.6)			
HBA1C					
Controlled	79(91.9)	7(8.1)	0.934	1	0.229
Uncontrolled	145(87.9)	20(12.1)			
FBS (mg/dl)					
□	153(88.4)	20(11.6)	0.375	1	0.355
<126	71(91.0)	7(9.0)			
BMI (kg/m²)					
< 30	156(90.7)	16(9.3)	2.770	1	0.081
□	68(86.1)	11(13,9)			

*$X^{2=}$ Chi Square, t= T-test, DF= Degree of freedom, * = Statistically significant*

Table V Association Between Serum Creatinine, PCV Proteinuria and Fasting Blood Sugar of the Subjects

	Serum Creatinine (freq(%))		Df	Sig	Proteinuria (freq (%)		Df	Sig	PCV (freq (%	
	H(n=30)	N (n-221)			+ve(n=21)	-ve(230)			Ln=53)	N (n=198)
FBS (mg/dl))										
□	21(12.1)	152(87.9)	1	0.538	20(11.6)	153(88.4)	1	0.003*	34(19.7)	139(80.3)
<126	9(11.5)	69(88.5)			1(1.3)	77(98.7)			19(24.4)	59(75.6)

H=High; N=Normal; L=Low; PCV=Packed cell volume, +ve=Positive, -ve=Negative, freq= Frequency, DF= Degree of freedom, *=Statistically significant, Sig=P-Value

Twenty-one of the subjects who had fasting blood level sugar level of ≥ 126 mg/dl also high serum creatinine. Twenty subjects (11.6%) with fasting blood level sugar level of ≥ 126 mg/dl had proteinuria 34(19.7%) of subjects with fasting blood level sugar level of ≥ 126 mg/dl had low PCV There was a statistically significant association between FBS and proteinuria (P≤0.05).

Table V1: Association between, PCV, HBA1C, Serum Creatinine, FBS, BMI and Early Marker of Nephropathy (Proteinuria)

Variable	Proteinuria (Freq (%) +VE (n=21) - VE(n=230)		X^2	Df	P-Value
PCV (%)					
Anemic	11(20.8)	42(79.2)	13.449	1	0.001*
Normal	10(5.1)	188(94.9)			
HBA1C					
Controlled	6(7.0)	80(93.0)	0.330	1	0.377
Uncontrolled	15(9.1)	150(90.9)			
Creatinine(mg/dl)				1	0.006*
Normal	14(6.3)	207(93.7)	9.955		
High	7(23.3)	23(76.7)			
FBS (mg/dl)					
□	20(11.6)	153(88.4)	7.409	1	0.003*
< 126	1(1.3)	77(98.7)			
BMI (kg/m²)					
□	11(6.4)	161(93.6)	2.770	1	0.081
>30	10(12.7)	69(87,3)			

*$X^{2=}$ Chi Square, DF= Degree of freedom, * = Statistically significant*

Table V11: Binary logistic between the predictors FBS, Creatinine, PCV and Proteinuria

Predictor	Coefficients	df	Sig.	Odd Ratio	95% C.I. for Odd Ratio Lower	Upper
FBS	2.604	1	.014	13.517	1.688	108.263
Creatinine	1.387	1	.014	4.002	1.324	12.093
PCV	1.6632	1	.001	5.276	1.976	14.081

DISCUSSION

Diabetic nephropathy has been implicated as the most fatal complication of diabetes mellitus (DM)) resulting in chronic kidney disease (CKD) and it is recognized as one of the leading causes of end-stage renal disease (ESRD) in the United States [3, 13]. The global prevalence is at an astronomical value of 40%. This study however seeks to determine the prevalence of diabetic nephropathy among diabetic nephropathy naive patients at early clinic visits at the endocrinology unit.

In this study, the mean age of the subjects was 56.2 ± 13.1 years. This was slightly lower than the average recorded in similar studies on the prevalence of diabetic nephropathy among Patients with Type 2 diabetes mellitus in China and Spain, however higher than the mean age recorded in another study conducted in Ethiopia with a mean age of 45 ± 14.5years [14, 15 16] with female gender preponderance of 1.35:1 *The* comparative increase in age difference

may be attributed to the higher prevalence of DM, large population of western world and their advanced Medicare. The study revealed a mean duration of diabetes of 10 ± 5.5years, this is lower than an average duration of 14.67 ± 10.6years submitted by Bleyer AJ et al [14,17] The longer duration of DM documented by Blayer et al could be because the European patients present early at endocrine clinic unlike what we observed in our clime.

Obesity and overweight have been reported to complicate DM and diabetic nephropathy in various pathogenetic mechanisms. These include free radical deposits in renal sinus, fat mediated by adiponectin, leptin, increased RAAS activation, in insulin resistance factor, development of glomerular hypertension and increased glomerular permeability and injury leading to glomerulosclerosis. Correspondingly, this research showed that 31.5% were obese, which is higher than the studies done in Ethiopia and some parts of Europe and Asians; Lu J, Liu X et al with a mean BMI of 23.3 and 24.8kg/m^2 for males and females respectively [16,17,18]

Glycemic control has been shown to play a pivotal role in the management of diabetes nephropathy. Poor glycemic control triggers multifactorial pathogenic mechanisms culminating in diabetic nephropathy. Hyperglycemia is known to activate inflammatory damage to the glomerular basement membrane and reno-vascular damage resulting in diabetic nephropathy mediated by reactive oxygen stress, RAAS, angiotensin 11 and cytokines. Findings from this study documented 34.3% of the patients had poor glycemic control with a mean HBA1C of 8.7± 2.9%. This was higher than the values obtained by Rodriguez-Poncelas A, Garre-Olmo J et. al who reported a mean of 7.3±1.3% as well as previous work on "discordance in risk factors for the progression of diabetic retinopathy and diabetic nephropathy in patients with type 2 diabetes mellitus"; reported mean in that study was 7.27±1.03% [15, 19.\] The comparative degree of poor glycemic control in our study was probably due to poor financial support to procure anti-diabetic medications thus poor level of compliance.

Anaemia has been established as part of the significant pathognomonic abnormalities associated with diabetes nephropathy, this study showed that 53(21.1%) of subjects had anaemia, conversely, in the study by Loutradis C et al, they concluded that the prevalence of anaemia progressively increased with advancing stages of CKD and was higher in diabetic than matched non-diabetic CKD patients with a corresponding prevalence of 53.5% of anaemia in CKD Stage 3 [12, 20]

The hallmark diagnosis of early diabetic nephropathy has been described by various researchers. Identification of persistent proteinuria has been discussed and established in previous studies using dipstick, which is sensitive, rapid, reliable and non-invasive. Persistent proteinuria is taken as an occurrence with urine dipstick taken at 2 or 3 times at least 4 weeks apart. Appearance of bedside dipstick proteinuria repeated in 2 different occasions is indicative of early signs of diabetes nephropathy. Findings from this study noted a proteinuria prevalence of 21(8.4%). Our study fairly correlates with the work of MA Aziz K [21] where he concluded that microalbuminuria strongly correlates with urine dipstick proteinuria findings in diabetic nephropathy. In similar studies where qualitative proteinuria (albustix) was used to assess clinical diabetic nephropathy, Alebiosu in Nigeria submitted a higher prevalence of 28.4% [22], In Tunisia 11% but South Africa reported a lower prevalence of 5.3%.[23]

The lower prevalence reported in our study may be due to comparatively small sample size. Other notable factors accounting for differences in the prevalence rate of proteinuria may be due to variations in study design, source of study population, sample selection, race, age, sex structure of the study population, diagnostic criteria, as well as the methods of measurement of proteinuria and urine collection, diabetic duration, presence of comorbidity such as hypertension and retinopathy [12, 24]

With progression in the level of proteinuria, the level of nephropathy worsens with the increased level of serum creatinine. Thirty (12.0%) had serum creatinine above 1.3mg/dl with most of the subjects in CKD 3. We also showed in the study that serum creatinine had no statistical significance with glycemic control. In contrast, Ethiopian and Spanish studies noted 18.5% and 27% respectively in similar stages with eGFR of 38 ml/min.

This research also showed that worsening renal function at eGFR less than 50 ml/min was significantly associated with anaemias but not observed to be significant with poor glycemic control, however, this is not in consonant with the established guidelines that reported the prevalence of kidney disease was fivefold greater among patients with uncontrolled diabetes compared with control 25,[26] Also in the work of Omani et al in type 2 diabetics at Al-dakhiliyah centre, he noted a

significant association between diabetic nephropathy and poor glycemic control (high HbA1c), [27]

There was a significant association between proteinuria, serum creatinine, fasting blood sugar and nephropathy (P≤0.05) Logistic regression results showed that subjects with FBS≥126mgdl are 14 times more likely to develop proteinuria with a confidence interval at 95% (1.688 - 108.263), subjects with serum creatinine ≥1.3mg/ dl were 4 times more likely to develop proteinuria with a confidence interval at 95% (1.324 - 12.093) while subjects with PCV less than 35% were 5 times more likely to develop proteinuria with a confidence interval at 95% (1.976 – 14.081).

Limitations

Our work was a hospital based cross sectional observational study, as some of our subjects had been on several anti-glycaemic medications and this could interfere with our outcome. Some of the subjects could not complete and afford investigations such as fundoscopy screening, microalbuminuria or albumin-creatinine ratio test which has been adjudged to be more sensitive in early diagnosis of DM nephropathy, this also affected the sample size. MDRD was found convenient to calculate the eGFR in the clinic but not the best parameter to capture subjects in early or advanced CKD. It was a single-centre study, so may not really reflect what is obtainable in other centres.

CONCLUSION

Our study submitted that about 10% of the patients who attended diabetic clinics already had clinical diabetic nephropathy without them knowing. It is therefore important to identify this susceptible group early to avert deterioration in renal function.

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