PROGRESSION OF DIABETIC NEPHROPATHY: A TWELVE-YEAR FOLLOW-UP OF TYPE2 DIABETIC PATIENTS

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ABSTRACT
Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) in advanced countries and the third commonest cause of ESRD in Nigeria. Management of diabetic ESRD adds additional economic and morbidity burden for the patient and the nation. The progression of DN can be retarded to delay commencement of renal replacement therapy if hyperglycemia, hypertension and proteinuria are controlled.

Twenty-two newly-diagnosed DN patients due to type2 diabetes mellitus (8 males and 14 females) were recruited for the study and followed up for 12 years. Their blood pressure (BP) and fasting blood sugar (FBS) were monitored quarterly at outpatient clinic visit while creatinine clearance (Crcl) and 24 hours urine protein excretion (UPE) were assessed annually. Results were reviewed at the end of study and compared with values at initiation of study. There was significant reduction in blood pressure (BP) from onset of study to end of follow-up (p< 0.001). There were significant reductions in systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (p<0.05). There was significant reduction in FBS (p<0.01). Proteinuria increased progressively and significantly (p<0.001) while Crcl decreased (p<0.001). The annual rate of increase in proteinuria was 0.077g while Crcl reduced at the rate of 5.13ml/min/1.73m2/year (p<0.001). Despite glycaemic and BP control, proteinuria increased while Crcl decreased over the years but at lower rates than predicted for proteinuric diabetic patients. None of the patients needed renal replacement therapy by the end of study.

Early and intensive glycaemic control, anti-hypertensive and anti-proteinuric therapies (use of angiotensin converting enzyme inhibitors-ACEIs and angiotensin receptor blockers-ARBs) can retard progressive nephropathy in Nigerian type2 diabetes mellitus patients.

Introduction
Diabetic nephropathy (DN) is a common chronic kidney disease (CKD) that complicates both type1 and type2 diabetic mellitus (DM)\(^1\)\(^-\)\(^3\). It occurs in about 40% of type2 DM and it is the leading cause of end-stage renal disease (ESRD) in Europe, Japan and United states\(^4\)\(^-\)\(^6\). It is the third most common cause of CKD in Nigeria\(^7\). In Europe, 94.9% of the diabetic population has type2 diabetes which makes it the most common type of diabetes mellitus\(^8\). Diabetic nephropathy is characterized by early microalbuminuria that coexists with hyperfiltration which progresses to macroalbuminuria (proteinuria), hypertension and eventually ESRD\(^9\)\(^-\)\(^13\). Microalbuminuria, hyperfiltration, proteinuria and hypertension constitute markers of progressive DN\(^14\)\(^-\)\(^16\). In a previous report Unuigbe et al identified these
markers in a significant population of newly-diagnosed type2 DM patients\(^\text{17}\). In type2 DM, established DN results in relentless decline in renal function to ESRD if not treated \(^\text{18,19}\). The Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetic Study (UKPDS) have reported that early intensive anti-hypertensive, anti-proteinuric and normoglycaemic measures reduced microalbuminuria, proteinuria and attenuated the rate of decline in glomerular filtration rate (GFR) \(^\text{2,3,20}\). The angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) exert anti-proteinuric and anti-hypertensive effects which can retard DN \(^\text{21,22}\).

The authors examined the effects of glycaemic control, anti-hypertensive and anti-proteinuric therapies in retarding the progression of DN among Nigerian type2 DM patients in a 12 years prospective study. The aims of treatment were to ensure strict glycaemic control, normalize blood pressure (BP \(\leq 130/80\) mmHg or MAP \(\leq 96\) mmHg), and reduce urine protein excretion (UPE) to less than 1.0g/24hrs as recommended for DN \(^\text{23}\). These measures were expected to prevent or limit further decline in Crcl to ESRD.

**Patients and methods**

Twenty-two newly diagnosed DN patients due type2 DM (classified by WHO 1985 diagnostic criteria\(^\text{24}\)) attending the outpatient clinic were consecutively recruited and followed up for 12 years at the University of Benin Teaching Hospital. The inclusion criteria for recruitment were dipstick positive proteinuria or 24hr UPE of \(\geq 0.5\) g and presence or absence of hypertension. Patients were excluded from study if there was evidence of cerebrovascular accident, previous myocardial infarction, heart failure and initial Crcl of \(\leq 30\) ml/min. There were 14 females and 8 males. Fourteen patients were diabetic and hypertensive (BP \(\geq 140/90\) mmHg) while 8 were diabetic only. The various parameters assessed at initiation of study were; body mass index (BMI: ratio of body weight (Bwt) in kg and height in meter\(^2\)), BP was measured with the standard mercury column sphygmomanometer and fasting blood sugar (FBS) in mg/dl was assayed using the glucose oxidase method. These parameters were assessed at presentation and at quarterly clinic appointments. The serum creatinine (Scr) in mg/dl was assayed by modified Jaffe reaction\(^\text{25}\). Creatinine clearance (Crcl) in ml/min was estimated annually by timed urine collection and calculated as UVP (where U is urine creatinine in mg/dl, V is volume of urine in ml/minute and P is Scr in mg/dl) or calculated by Cockcroft-Gault formula ([140-Age in yrs] x Bwt (kg) / [72 x Scr]) \(\times\) 0.8 (if female). The 24hr UPE (in g) was assayed annually by trichloroacetic acid Pesc and Strande technique\(^\text{26}\). The patients were on oral hypoglycemic drugs (metformin and a sulphonylurea) and various anti-hypertensive agents suitable to control BP (with minimal side effects) were used for the hypertensive patients. An ACEI (lisinopril or captopril) and other antihypertensive drugs such as diuretics (amiloride + thiazide), minizide (prazocin + polythiazide) and calcium channel blockers (nifedipine or amlodipine) were administered to the patients. All the patients received an ACEI.

**Analysis of data**

The SPSS statistical package version 10 was used for analysis of data. The mean and standard deviation of the baseline characteristics were calculated and presented in the tables. Regression analysis and one way analysis of variance (ANOVA)
was done for serial values of the respective parameters monitored over the years. P value < 0.05 was considered significant.

Results
Twenty-two DN made up of 14 females and 8 males aged between 36 and 73yrs (mean age 52.75±10.90 years) were studied over a 12-year period. Table 1 shows the characteristics of study population at time of recruitment. Their BMI was 25.32±3.87, mean SBP was 146.32±5.3mmHg, mean DBP was 87.9±2.57mmHg and MAP was 107.00±15.40mmHg. Mean FBS was 161.95±18.09 mg/dl, mean Crcl 90.4±43.8ml/min and mean UPE was 0.74±0.20g/24hr. The comparison of baseline data with values after 12 years showed that there were significant reductions in mean SBP, DBP, MAP, FBS and Crcl while there was significant increase in the 24hr UPE (table 2). The regression graph for MAP showed a decreasing trend that was not significant (r = 0.467 for p>0.05, fig 1). The regression of 24hr UPE showed significant positive correlation over time (r = 0.891 for p<0.05, fig 2). Mean UPE increased from an initial value of 0.74±0.20 to 1.68±0.73g while the annual rate of increase in UPE was 0.077g (fig 2). The Crcl decreased progressively and significantly (r = 0.995 for p<0.01, fig 3). It decreased from an initial mean value of 90.4±43.8ml/min/1.73m² to 30.80±15.3ml/min/1.73m². The annual rate of decrease in Crcl was 5.134ml/min/year. There was no significant correlation between Crcl and UPE (r = -0.268 for p>0.05), however, interposing graphs of UPE and Crcl regression, the lines cross each other when UPE is about 1gm/24 hours and Crcl about 50mls/min (fig 4). Similarly there was no significant correlation between Crcl and MAP (r = 0.127 for p>0.05) nor between MAP and UPE (r = -0.090 for p>0.05).

Table 1: Characteristics of study population at time of recruitment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Range</th>
<th>Mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>36-73</td>
<td>52.75±10.90</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>1-14</td>
<td>2.82±3.20</td>
</tr>
<tr>
<td>BMI</td>
<td>18.6-30.30</td>
<td>25.32±3.87</td>
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<tr>
<td>SBP (mmHg)</td>
<td>110-220</td>
<td>146.32±5.3</td>
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<tr>
<td>DBP (mmHg)</td>
<td>70-110</td>
<td>87.89±2.57</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>90-129</td>
<td>107.00±15.40</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>65-382</td>
<td>161.95±18.09</td>
</tr>
<tr>
<td>Crcl (ml/min)</td>
<td>30-169.2</td>
<td>90.4±43.8</td>
</tr>
<tr>
<td>24hrUPE (g)</td>
<td>0.05-2.9</td>
<td>0.74±0.20</td>
</tr>
</tbody>
</table>

BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure

MAP = mean arterial pressure, FBS = fasting blood sugar, Crcl = creatinine clearance, UPE = urinary protein excretion
Table 2: Comparison of mean baseline values of parameters with values at the end of study

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Baseline values</th>
<th>End of study</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>146.32±5.3</td>
<td>123.7±6.7</td>
<td>&lt;0.05</td>
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<tr>
<td>DBP (mmHg)</td>
<td>87.9±2.57</td>
<td>81.33±3.33</td>
<td>&lt;0.05</td>
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<tr>
<td>MAP (mmHg)</td>
<td>107.00±15.4</td>
<td>96.7±5.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FBS (mg/dl)</td>
<td>162.0±18.1</td>
<td>66.0±0.00</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24hr UPE (g)</td>
<td>0.74±0.2</td>
<td>1.68±0.73</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Crcl (ml/min)</td>
<td>90.4±43.8</td>
<td>30.8±15.3</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure, DBP = diastolic blood pressure, MAP = mean arterial pressure
FBS = fasting blood sugar, UPE = urinary protein excretion, Crcl = creatinine clearance

Fig 1. Regression of MAP over the years

MAP = mean arterial pressure

Fig 2. Regression of 24hr UPE over the years
UPE = urinary protein excretion
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Fig 3. Regression of Crcl over the years

Crcl = creatinine clearance

Fig 4. Regression of 24hr UPE and Crcl over the years

UPE = urinary protein excretion, Crcl = creatinine clearance
Discussion
In a previous report, the need for early detection of markers and prevention of progressive DN was emphasized by Unuigbe et al. It has been established that care for ESRD imposes a huge economic burden on the advanced economies, even more so if ESRD is due to DN because of additional co-morbid factors such as vascular disease, dyslipidaemia and the need for pancreatic transplant for diabetic ESRD.

Proportion of diabetics with renal disease is on the increase in Nigeria and portends obvious danger to our economy and this underscores the need for aggressive retardation of DN. Blood sugar and blood pressure of study population were significantly lower at end of study compared to values at commencement of study. Although, HbA1c was not assessed in this study because facilities for this was not readily available when study was done, we suggest that glucose control in addition to BP reduction retarded DN among the patients studied. This trend has been reported in the DCCT and UKPDS studies.

The patients studied had macroproteinuria at recruitment, increased progressively and significantly at a rate of 0.077g/year. ACEIs can be used and are recommended in DN patients inorder to reduce and maintain UPE to values less than 1.0g/24hrs. Although this value was not achieved in the study population UPE remained significantly less than nephrotic range at end of study. Urinary protein excretion was inversely related to Crcl in the study population. This finding agrees with an earlier report that increasing proteinuria maybe the determinant factor for progressive DN. We suggest that it may be necessary to keep UPE at a value less 1.0g/24hrs in order to prevent further decline in Crcl beyond approximately 50ml/min as UPE values above 1gm/24 hours may be associated with further decrease in Crcl.

It has been predicted that Crcl will decline at the rate of 12ml/min/year in untreated DN but in this study Crcl declined at the rate of 5.13ml/min/year and mean Crcl at the end of study was 30.8±15.3ml/1.73m²/min.

Although proteinuria and Crcl worsened overtime, none of the patients progressed to ESRD or needed renal replacement therapy during the 12-year period. In the absence of intervention and with Crcl declining at 12ml/min/year, patients would have developed ESRD about 5 years after recruitment. The mechanisms that mediate development and progression of DN appear to be complex and inconclusive.

Treatment should contend with proteinuria, increased glomerular capillary hydraulic pressure and systemic hypertension. Experimental studies have shown that proteins filtered by the glomeruli induce proliferation of proximal tubular cells with increased synthesis of vaso-active and pro-inflammatory substances. Renin-angiotensin system and growth factors mediate structural and functional changes during the course of DN and are responsible for intra-glomerular and systemic hypertension. Maki et al have reported that any antihypertensive measure is capable of reducing proteinuria and that each 10mmHg reduction in BP decreases proteinuria by 14%. The UPE reduction rates of various antihypertensive drugs have been rated as follows; ACEIs and ARBs 45%, nondihydropyridine calcium channel blockers 35% and conventional antihypertensive drugs 23%. ACEIs can
induce 23% proteinuria reduction without change in BP\textsuperscript{34}. The economic benefits of limiting progressive DN are far reaching for the individual, family and national workforce of a developing economy as ours. Every type2 DM patient, at first presentation, should be managed as a case of progressive DN because most would have passed the stage of hyperfiltration\textsuperscript{17}. Although the target UPE was not achieved, the ACEIs used in these patients may have contributed to reduction of UPE in them. We also advocate for more frequent monitoring of renal function, at least quarterly.

Conclusion
In conclusion, blood sugar and blood pressure control contributed to the slow progression of proteinuria and slow decline in renal function in this study. We advocate that physicians adhere to the recommendation that ACEIs and ARBs be included in treatment regimes at the initiation of treatment for both normotensive and hypertensive diabetics with or without proteinuria.

References


