Assessment for markers of nephropathy in newly diagnosed type 2 diabetics

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Summary
Background: Type 2 diabetics account for a large proportion of patients presenting in end-stage kidney disease (ESKD). Although diabetic renal disease can be predicted, a lot of diabetics present to Nephrologists in ESKD.
Objective: To assess for markers of nephropathy in newly diagnosed type 2 diabetics, using blood pressure levels, endogenous creatinine clearance and urinary protein excretion as markers of renal disease.
Study design: Ninety newly diagnosed type 2 diabetics were studied within 6 weeks of diagnosis. They were in good glycemic control during the period of study. Seventy-two age and sex-matched and apparently healthy non-diabetics served as controls. Blood pressure was recorded in all subjects. 24 hours urine sample was collected for estimation of urinary protein excretion and endogenous creatinine clearance.
Results: Systolic and diastolic blood pressures were consistently higher in diabetics than in controls (p=0.001 and p=0.001 respectively). High-normal and mildly elevated blood pressure were more prevalent in diabetics (p=0.001). Mean creatinine clearance in diabetics was significantly lower than in non-diabetics (p=0.037). 7% of diabetics had supra-normal creatinine clearance of >125 mls/minute. The prevalence of microproteinuria was 40% in diabetics and 33% in non-diabetics, while macroproteinuria was present in 44% of diabetics but absent in non-diabetics (p=0.000)
Conclusion: High-normal, mildly elevated blood pressure and microproteinuria were commonly encountered in newly diagnosed diabetics studied. The phenomenon of hyperfiltration was present in type 2 diabetics. These tools should be assessed at diagnosis of diabetics as this will help in identifying those who are at an increased risk for developing diabetic nephropathy.

Key-words: Diabetics, Blood pressure, Proteinuria, Hyperfiltration, Nephropathy.

Rezumé
Introduction: Diabétiques type 2 constitue un grand nombre de patients qui s'inscrivent atteints de la maladie du rein dernière étape, (MRDE), Quoique la maladie diabétique rénale soit prévisible, un grand nombre de cas des patients diabétiques atteints du MRDE se présentent au près des Néphrologistes.
Objectif: Évaluer pour les marqueurs de la néphropathie chez des diabétiques type 2 nouvellement diagnostiqués avec l'utilisation des niveaux de la tension artérielle, la clairance de la créatinine endogène et l'excrétion de la protéine urinaire comme des marqueurs de la maladie rénale.
Plan d'étude: Quatre vingt dix des diabétiques type 2 nouvellement diagnostiqués ont été étudiés au cours de six semaines du diagnostic. Ils étaient tous en très bon état du contrôle glycémique pendant la période d'étude. Âgé de 72 ans et sexe bien assorti et non diabétiques apparemment en très bonne santé utilisés comme des contrôles: On avait noté la tension artérielle chez tous les sujets. On avait eu une collection d'un échantillon d'urine pendant 24 heures pour une évaluation d'excrétion de la protéine urinaire et la clairance de la créatinine endogène.
Résultats: La tension artérielle systolique et diastolique ont été bien élevées de manière cohérente chez les diabétiques plus que chez des contrôles (P=0.001 et P=0.001 respectivement). Élevé moyen et tension artérielle moyennement élevée ont été très répandues chez des diabétiques (P=0.001). La clairance de créatinine moyenne chez des diabétiques étaient sensiblement bas plus que chez des non diabétiques (P=0.037), 7% des diabétiques avaient la clairance de la créatinine supra-moyenne de >125 mls/minute. La prévalence de la microprotéinurie était 40% chez des diabétiques et 33% chez des non-diabétiques, tandis que la macroprotéinurie était présent en 44% des diabétiques mais absent chez des non-diabétiques (P=0.000)
Conclusion: Élevé moyen, la tension artérielle moyennement élevée et la microprotéinurie ont été ordinairement éprouvées chez des diabétiques nouvellement diagnostiqués études. Le phénomène d'hyperfiltration était présent chez des diabétiques type 2. On doit évaluer ces outils pendant le diagnostic des diabètes parce que ceci va aider à provoquer l'identification de ceux qui sont à l'augmentation de risque pour le développement de la néphropathie diabétique.

Introduction
Diabetic kidney disease is now the most common cause of end-stage kidney disease (ESKD) in the United States and accounts for a large proportion of patients beginning dialysis therapy. The risk of overt nephropathy and ESKD was thought to be uncommon in type 2 diabetics but recently kidney disease in type 2 diabetics has assumed appreciable proportions in the United States and elsewhere and both types 1 and 2 diabetics now seem to have a similar risk of developing nephropathy.
Up until two decades ago diabetes mellitus was reported to be an uncommon cause of chronic kidney disease in Nigeria but in the last few years, reports from several Renal Units in the country now place diabetic nephropathy as the third most common cause of chronic renal failure. Microalbuminuria (MA), glomerular hyperfiltration and hypertension are markers for renal events in diabetes and their presence predict development of clinical diabetic nephropathy. As a fall out of this, many now advocate preventive nephrology in the care of diabetics and this involves the search for markers for kidney disease. Where such markers are identified and intervention strategies are put in place, the eventual development of ESKD can be retarded or slowed down.

The aim of this study, therefore, was to assess the prevalence of some markers for renal events, such as hypertension, microproteinuria and hyperfiltration in newly diagnosed type 2 diabetics.

Patients and methods

A total of 90 newly diagnosed type 2 diabetics attending the University of Benin Teaching Hospital were consecutively recruited and studied within six weeks of diagnosis. Type 2 diabetes mellitus was diagnosed on clinical grounds using the World Health Organisation (WHO) criteria for the diagnosis and classification of diabetes mellitus. Patients with previous history of hypertension or renal disease were excluded. Healthy subjects with no history of diabetes mellitus, hypertension or renal disease served as controls. They were age and sex matched with the diabetics.

Bio-data and blood pressure readings were recorded in all subjects. With patients in a sitting and relaxed position blood pressure was measured in all subjects by one observer. Readings were classified using the WHO/ISH Hypertension Guidelines.

Diabetics were in good glycaemic control during the period of study with fasting blood glucose range of 80-110mg/dL and/or 2 hours post-prandial glucose of 120-140mg/dL. Urine was collected over twenty-four hours in all subjects for estimation of urinary protein and endogenous creatinine clearance. Venous blood sample for serum creatinine estimation was obtained from subjects during the period of urine collection or immediately after. Urinary protein was measured using the trichloroacetic acid Pesce and Strand technique while serum and urine creatinine were measured by the Jaffe reaction method. Urinary protein excretion of <150mg/24hrs was regarded as normal protein excretion, 150-500mg/24hrs and >500mg/24 hours were taken as microproteinuria and macroproteinuria respectively. Serum creatinine of 1.5–3.0mg/dL and >3mg/dL were regarded as chronic renal insufficiency and chronic renal failure respectively. Creatinine clearance was calculated using the formula UV/P, where U is urine creatinine mg%, V is volume of urine per minute and P is plasma creatinine mg%. A creatinine clearance of >125mls/minute was regarded as supranormal or glomerular hyperfiltration.

Data are presented as mean ±SD and percentages. Student’s t-test was used to compare means and Chi-squared test to compare proportions. P values<0.05 were considered significant.

Results

Ninety newly diagnosed diabetics (46 males, 44 females) aged 36 – 75 years (mean 53.44 ± 10.76 years)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetics (N=90)</th>
<th>Non-Diabetics (N=72)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.44±10.76</td>
<td>52.75±9.30</td>
<td>0.09</td>
</tr>
<tr>
<td>Prevalence of high normal BP</td>
<td>24(27%)</td>
<td>16(22%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prevalence of elevated BP</td>
<td>20(23%)</td>
<td>0(0%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>129.73±15.12</td>
<td>122.50±11.98</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.04±9.62</td>
<td>79.17±7.51</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>76.38±32.60</td>
<td>85.10±14.57</td>
<td>0.037</td>
</tr>
<tr>
<td>Urinary protein excretion (mg/24hrs)</td>
<td>706.23±623.64</td>
<td>165.55±81.21</td>
<td>0.000</td>
</tr>
<tr>
<td>Prevalence of microglobulin</td>
<td>36(40%)</td>
<td>24(33%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Prevalence of macroproteinuria</td>
<td>40(44%)</td>
<td>0(0%)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Plus, minus values are means ±SD.
Chi-squared tests were calculated with Yates correction.
and 72 non-diabetics (36 males, 36 females) aged 37 – 75 years (mean 52.75 ± 9.3 years) were studied.

Characteristics of diabetics and non-diabetics are shown in Table 1. Mean blood pressure, prevalence of high normal and elevated blood pressure were consistently higher in diabetics. 46 (51%) diabetics and 56 (78%) non-diabetics had normal blood pressure. High normal blood pressure was encountered in 24 (27%) diabetics and 16 (22%) non-diabetics while elevated blood pressure in the range of mild hypertension was seen in 20 (22%) diabetics and no control subject (p=0.001). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly higher in diabetics compared to non-diabetics. Mean SBP was 129.73 ± 15.12 mmHg and 122.50 ± 11.98 mmHg in diabetics and non-diabetics respectively (p=0.001) while mean DBP was 85.04 ± 9.62 mmHg in diabetics and 79.17 ± 7.51 mmHg in non-diabetics (p=0.001).

Renal function was poorer in diabetics than non-diabetics. 23% and 2% of diabetics and non-diabetics respectively had chronic renal insufficiency, while 2% of diabetics and none of the controls had chronic renal failure. Endogenous creatinine clearance (CrCl) ranged from 3.8–136 mls/minute in the diabetic subjects and 39.58–103.75 mls/minute in non-diabetics. Mean CrCl of 76.38 ± 32.60 mls/minute in diabetics was significantly less than that of 85.10 ± 14.57 mls/minute in non-diabetics (p=0.037), 6 diabetics (7%) had supranormal CrCl of >125 mls/minute.

Urinary protein excretion (UPE) was significantly higher in diabetics compared to non-diabetics. Mean UPE was 706.23 ± 623.64 mg/24 hours in diabetics and 165.55 ± 81.21 mg/24 hours in non-diabetics (p=0.000). 14 (16%) diabetics and 48 (67%) non-diabetics had normal UPE while 36 (40%) diabetics and 24 (33%) non-diabetics had microproteinuria. 40 (44%) of diabetics while none of the controls were macroproteinuric (p=0.000). No subject in the study population had proteinuria in the nephrotic range.

Discussion

The cost of caring for diabetic patients who develop ESKD is more than that for non-diabetic patients with ESKD because of the presence of co-morbid factors like vascular disease and dyslipidaemia in the former. Prevention of diabetic nephropathy, including its early detection, is therefore more fulfilling and less expensive to both diabetics and national budgets. Although, the increasing contribution of diabetes mellitus to development of ESKD in Nigerians patients is no longer in doubt, preventive measures, particularly the search for markers are not yet routinely or widely practised.

High blood pressure has the effect of increasing albumin levels in type 2 diabetics who start off with normal albumin levels and this can be prevented or limited by the adequate use of anti-hypertensives. Appreciable proportions of diabetics studied had high normal blood pressure and mild hypertension (27% and 22%) respectively. Though lower than 30% and 80% hypertension rates reported by Mogensen and Keller et al respectively in newly diagnosed type 2 diabetics, our findings are worrying enough to spur clinicians into action. The use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in diabetics above with high normal blood pressure and mild hypertension will give rewarding results as their use in such patients have been reported to be beneficial.

Diabetes with microalbuminuria has an increased risk of renal complications even before glomerular filtration begins to reduce. Proteinuria occurred commonly in diabetics studied and specifically, microproteinuria was encountered in 40% of diabetic subjects. These findings of microproteinuria and high normal blood pressure/ elevated blood pressure will act in synergy and hasten development of nephropathy in this group of diabetics. Intervention measures to prevent progression of microproteinuria to macroproteinuria are called for in such diabetics where above normal blood pressure levels are coexisting with proteinuria as reports have suggested that macroproteinuria helps to speed progression of diabetic kidney disease and other proteinuric kidney disease. Apart from their blood pressure lowering effects in hypertensive diabetics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been found useful even in normotensive diabetics for reducing proteinuria and slowing down progression of microalbuminuria to macroalbuminuria.

Although, the clinical features of nephropathy in type 1 and 2 diabetics are similar, the course of nephropathy differs in the two groups. In type 1 diabetes mellitus, onset of disease is abrupt, course of nephropathy is well defined with clinical nephropathy developing 15 years to 25 years after onset of diabetes and nephropathy eventually resulting into ESKD. Type 2 diabetes, on the other hand, has an insidious onset, the course of nephropathy is not so well defined because of the presence of confounding variables such as advanced age, coexistence of vascular disease and hypertension. Hence the clinical course of diabetic nephropathy is best exemplified with type 1 diabetes and most of the facts in literature about diabetic nephropathy have emanated from work done on type 1 diabetes. Glomerular hyperfiltration has been reported in newly diagnosed diabetics and this phenomenon occurs during periods of hyperglycaemia following diagnosis of diabetes. The haemodynamic changes that accompany the hyperfiltration are thought to contribute to the development of diabetic nephropathy. Earlier works, though few, suggest that glomerular hyperfiltration also occurs in type 2 diabetes. Our findings support these reports as supranormal creatinine clearance and hence hyperfiltration was present in 7% of diabetics studied. The hyperfiltration reported in type 1 diabetics is not sustained in the presence of near normal glycaemia. Christiansen et al studying newly diagnosed type 1 diabetics reported elevated glomerular filtration rates (GFR) at time of diagnosis but following
treatment with multiple subcutaneous insulin and subsequent near normal blood glucose, they noted a significant reduction in the GFR in the diabetics. This study was done when diabetics had good glycaemic control and probably some cases of supranormal creatinine clearance may have been missed, hence the not so large proportion of diabetics in this study with hyperfiltration. Also the fact that type 2 diabetics present insidiously may have contributed to “missed” cases of hyperfiltration in diabetics studied. We suggest that a good proportion of them may have gone past the stage of hyperfiltration before the clinical diagnosis of diabetes mellitus. Although newly diagnosed and with no previous history of renal disease, as many as 23% and 2% of the diabetic subjects had renal insufficiency and chronic renal failure respectively. This probably is because the diabetics studied may have had sub-clinical diabetes, which was having its toll on the kidneys even before the clinical diagnosis of diabetes mellitus.

In conclusion, our study shows that markers for the development of nephropathy are present in newly diagnosed type 2 diabetics and that glomerular hyperfiltration also occurs in this group of diabetics.

References


