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Full Length Research Paper

The Usefulness of Urinary Fibronectin as an Early Marker of Glomerular Injury in Type 2 Diabetes Mellitus Patients

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About one-third of diabetes is complicated by diabetic kidney disease. It is even challenging in type 2 diabetics in which this complication may occur before the presentation. Traditionally, microalbuminuria is the first marker of early diabetic kidney disease. However, it has many limitations, including developing when significant kidney damage has already occurred. This study aimed at determining the urinary fibronectin excretion levels in type 2 diabetic without complications and in the control group. This was a hospital-based cross-sectional study, consisting of 120 type 2 diabetics without complications and 120 apparently healthy non-diabetic/hypertensive as controls. Microalbuminuria was measured using Immunoturbidimetric assay while urinary fibronectin was measured using ELISA technique. Statistical analysis was done using statistical package for social science version 20. A p-value of less than 0.05 was considered statistically significant. Urinary fibronectin was significantly higher in type 2 diabetics in comparison to the control group (1.29 ± 1.69 µg/ml vs 0.29 ± 0.31 µg/ml, p < 0.001). Based on Albumin-Creatinine-Ratio, 27.5% of the type 2 diabetics were micro albuminuric as compared to none in the controls. There was a significant positive correlation between urinary fibronectin and microalbuminuria (r- 0.23; p= 0.013). The sensitivity of urinary fibronectin was 93.9%, negative predictive value was 77.8% and area under the curve of 0.0830 in the receiver operating characteristics (ROC) curve. Urinary fibronectin is a useful early biomarker in the renal evaluation of type 2 diabetics.

Keywords: Diabetic Kidney Disease, Microalbuminuria, Urinary Fibronectin.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by chronic hyperglycaemia caused by absolute or relative insulin deficiency or defective action or both, resulting in disorders of carbohydrate, protein and fat metabolism (Chinenye, 2011). It is associated with long-term damage, dysfunction, and failure of various organs especially the eyes, kidneys, nerves, heart, and blood vessels. They are termed micro-vascular complications.

Diabetic kidney disease is one of the most challenging micro-vascular complications with significant impact on morbidity, mortality and quality of life (Hellemons *et a*l., 2012). Diabetic kidney disease or diabetic nephropathy (DN) is a clinical syndrome which is characterized by persistent albuminuria, a continuous decline in glomerular filtration rate (GFR), intra – renal hypertension and increased relative mortality from cardiovascular diseases (Rehman, 2004). Diabetic nephropathy occurs approximately in one–third of individuals with type 1 and type 2 diabetes mellitus (Rehman *et al*., 2005). Risk factors for the development of diabetic nephropathy include hyperglycaemia, hypertension and smoking (Timothy *et al* 2008). Patients with reduced renal functional reserve capacity may be more prone to microalbuminuria when exposed to conditions such as hyperglycaemia or hypertension (Horvino et al., 2004). Diabetic nephropathy (DN) is the

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major leading cause of kidney failure in the world and occurs in about one – third of diabetic patients (World Health Organization, 2016). Death resulting from kidney disease is 17 times more common in diabetes mellitus than in non-diabetics (Hong, 1998). Alebiosu and Ayodele (2006) reported the increasing prevalence of diabetic nephropathy as a cause of end-stage kidney disease in Nigeria (Alebiosu, 2006).

Multiple biomarkers of kidneys injury in serum and urine have been studied. These biomarkers have been classified as markers of glomerular injury, oxidative stress inflammation or endothelial damage based on the different ways of structural damage to the kidneys which they represent (Matheson *et al*., 2010). The urinary markers of glomerular injury are caused by either increased permeability to plasma proteins (albumin, transferrin, ceruloplasmin etc) or increased excretion of extracellular matrix proteins like fibronectin (Lahmann, 2000).

Clinically, the first sign of diabetic kidney (diabetic nephropathy) is considered to be microalbuminuria. As the disease progresses, patients develop macroalbuminuria and the kidney function declines until patients end up requiring renal replacement therapy (Remuzzi *et al*.,2002). Although microalbuminuria in diabetes is considered to be the best predictor of progression to end-stage renal disease (Zeeuw *et al.,* 2006) and cardiovascular events (Ninomiya *et al*., 2007), it has limitations and studies have suggested that microalbuminuria occurs when there is significant renal damage (Viberti *et al*., 1982; Scherberich *et al* 1994). The most abundant plasma protein in the body is albumin, it is produced in the liver and has a molecular weight of 65-kDa. In normal subjects, albumin molecules are too large to cross the glomerular basement membrane; only a small amount is filtered and it is almost completely reabsorbed by tubules, hence it is usually present in low concentration in urine (Haraldson *et al* 2008; Venturoli *et al*., 2006). Elevated urine albumin excretion rate (UAER) is considered a well established marker of glomerular damage (Anderson *et al*., 1998). Based on the ability of the dipstick to measure urine albumin, the UAER has been classified as microalbuminuria, when the UAER is between 30 – 300 mg/day or 20 – 200 µg/min; macroalbuminuria, when UAER is above 300 mg/day or 200 µg/min. Because of the inconsistencies, cumbersomeness and errors associated with the above methods, UAER is better classified using the albumin-creatinine-ratio (ACR). When the ACR is ≥ 3.5-25 (female) or ≥ 2.5-25 (male), it is classified as microalbuminuria and macroalbuminuria when > 25 in both sexes (Caramori *et al*., 2006).The rate of progression from micro to macroalbuminuria in type 2 diabetic patients is 2-3% annually (Adler *et al*., 2003). Microalbuminuria is a risk factor for end-stage kidney disease and also a predictor of cardiovascular mortality and morbidity in diabetic patients (Lahmann *et al*., 2000). Traditionally, microalbuminuria is regarded as the best marker for renal damage in diabetic patients, but, it has certain limitations. For example, 20% of diabetic patients with renal impairment have normal microalbuminuria (Birn *et al*., 2006). Also the renal and cardiovascular morbidity is elevated in the “high normal” range of UAER (Adler *et al* 2003; Wachtell *et al*., 2003)

Fibronectin is produced by the hepatocytes of the liver, it is a high molecular weight glycoprotein (440kDa) and a component of the glomerular matrix (Pankor *et al*., 2002). Fibronectin is a marker of early diabetic kidney disease (Scherberich et al., 1994). A study done by (Kananchi *et al*.,1995) revealed that urinary fibronectin excretion is higher in diabetic patients compared to controls but the difference is significant for diabetics with microalbuminuria (Kannchii *et al*., 1995). Additionally, urinary fibronectin levels correlate well with the progression of biopsy proven glomerular diffuse lesion.

Studies suggest that diagnosing diabetic kidney disease should be attempted before the microalbuminuria stage (when it might already be late) and urinary fibronectin excretion has been shown to be elevated in diabetic patients before the development of microalbuminuria (Scherberich *et al*., 1994). It then follows that earlier, more sensitive and specific markers of kidney damage might help in the diagnosis of diabetic kidney. Thus, facilitating the treatment of diabetic kidney disease at an earlier stage to prevent the progression to renal failure. This study, therefore, investigated the usefulness of urinary fibronectin as an earlier sensitive and specific biomarker for diabetic kidney disease among patients with type 2 DM in comparison to microalbuminuria. Furthermore, there is no literature yet in Nigeria on studies with urinary fibronectin on type 2 Diabetes Mellitus patients.

MATERIALS AND METHODS

Subjects

This is a hospital based cross-sectional study, carried out at the diabetic clinic of the University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria. One hundred and twenty diabetic patients (57 men and 63 women) with ages ranging from 24 – 74 years (mean age 51.30 ± 11.06) were included in this study The control group comprised of one hundred and twenty apparently healthy non-diabetic/hypertensive subjects (51 men and 69 women) with mean age 49.88 ± 11.30. Type 2 diabetics with hypertension, kidney disease, nephrotic syndrome, systemic hypertension or overt renal disease with frank proteinuria were excluded from the study.

Analytical methods

About 5- 6 ml of the venous sample were obtained from the antecubital vein in the morning after an overnight fast for measurements of fasting plasma glucose, plasma creatinine, using the glucose oxidase method and modified Jaffe method respectively. Early morning urine samples were collected for determination of urinary fibronectin, microalbuminuria and urine creatinine using ELISA technique, immunoturbidimetric assay and modified Jaffe method respectively.

The blood specimens were centrifuged at 1000 mg for 10 minutes. Plasma for glucose was analyzed daily, while plasma for creatinine was stored in the refrigerator for analysis in batches every other day. Urine samples from a 20 ml sterile bottles were aliquoted in plain specimen bottles for urinary fibronectin estimation and centrifuged at 800 mg for 10 minutes and stored at -20^{o}C for weekly batch analyses while the remainder was used daily for microalbuminuria and urine creatinine estimation.

Urinary fibronectin was measured quantitatively with Abcam Human Fibronectin Elisa kit(330 Cambridge Science Park, Cambridge CB4 OFL, UK). The assay is an in vitro competitive ELISA method. A polyclonal antibody specific for fibronectin has been pre-coated onto a 96-well microplate. Fibronectin in standards and samples was added to the wells and subsequently, a biotinylated polyclonal antibody specific for fibronectin was added and then followed by washing with wash buffer, which was recognized by a streptavidin-peroxidase conjugate. All unbound materials were then washed and TMB was added to visualize streptavidin-peroxidase enzymatic reaction. The colour development was stopped and the intensity of the colour was measured at 450nm. The colour changes from blue to yellow and the intensity of the yellow coloured product is inversely proportional to the amount of human fibronectin in the sample that was captured in the microtitre wells.

The amount of urinary albumin was measured by immunoturbidimetric assay (Biolabo SA laboratories, 02160, Maizy, France). Fasting plasma glucose, plasma and urine creatinine were assayed using Randox kit (Randox Laboratories Limited, 55 Diamond Road, Crumlin, Co.Antrim, UK BT 294QY).

STATISTICAL ANALYSIS

Data analysis was done using the statistical package for social sciences (SPSS) version 20. Means and standard deviations were calculated and student's t-test was used for assessing statistical differences between groups. Validity tests were carried out in form of sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The usefulness of urinary fibronectin as an early marker of diabetic kidney disease in relation to microalbuminuria was assessed using the receiver operator characteristics (ROC) curve. A p-value of less than 0.05 was considered statistically significant. The study was approved by the Ethical and Research Committee of the University of Port Harcourt Teaching Hospital, Port Harcourt.

RESULTS

Fibronectinuria was significantly higher in type 2 DM patients groups in comparison to the control group (1.29 ± 1.69 µg/ml vs 0.29 ± 0.31 µg/ml, $p < 0.001$). Table 1 shows the biochemical characteristics of type 2 DM patients and the control group.

Table 2 shows the proportion of subjects with microalbuminuria using ACR. Eighty-seven (72.5%) of type 2 DM patients had normal ACR as compared to 120 (100%) of the control group, while 33 (27.5%) and type 2 DM had microalbuminuria as compared with none in the control group, and this difference was statistically significant ($p < 0.001$).

The Pearson's correlation coefficient between urinary fibronectin and microalbuminuria in the entire study population was significantly positive ($r=0.23$; $p=0.013$).

Validity tests were done using microalbuminuria as the gold standard for diabetic nephropathy. The sensitivity was of urinary fibronectin was 93.9%, specificity was 8.0%, positive predictive value (PPV) was 27.9% while the negative predictive value (NPV) was 77.8% (Table 3 and Figure 1).

$$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive + false negative}} \times \frac{100}{1}$$

$$= \frac{31}{31+2} \times \frac{100}{1}$$

$$= \frac{31}{33} \times \frac{100}{1} = 93.9\%$$

$$\text{Specificity} = \frac{\text{True negative}}{\text{True negative x false positive}} \times \frac{100}{1}$$

$$= \frac{7}{7+80} \times \frac{100}{1}$$

$$= \frac{7}{87} \times \frac{100}{1} = 8.0\%$$

$$\text{PPV} = \frac{\text{True positive}}{\text{True positive + false positive}} \times \frac{100}{1}$$

$$= \frac{31}{31+80} \times \frac{100}{1}$$

$$= \frac{31}{111} \times \frac{100}{1} = 27.9\%$$

Table 1. Biochemical characteristic (mean ± SD) of type 2 DM patients and the controls.

Variables	Type 2 DM (n = 120)	Controls (n = 120)	P - value
FPG (mmol/L)	10.35 ± 5.53	4.97 ± 0.81	< 0.001
Plasma Creatinine (mmol/L)	89.33 ± 21.75	71.58 ± 9.10	< 0.001
Urine Creatinine (mmol/L)	27.04 ± 5.68	19.45 ± 2.44	< 0.001
Microalbuminuria (mg/L)	59.92 ± 97.37	2.11 ± 6.56	< 0.001
Urinary Fibronectin (µg/mL)	1.29 ± 1.69	0.20 ± 0.31	< 0.001
eGFR (ml/min)	97.35 ± 99.72	113.13 ± 18.81	0.090

FPG: Fasting Plasma Glucose; eGFR: Estimated Glomerular Filtration Rate

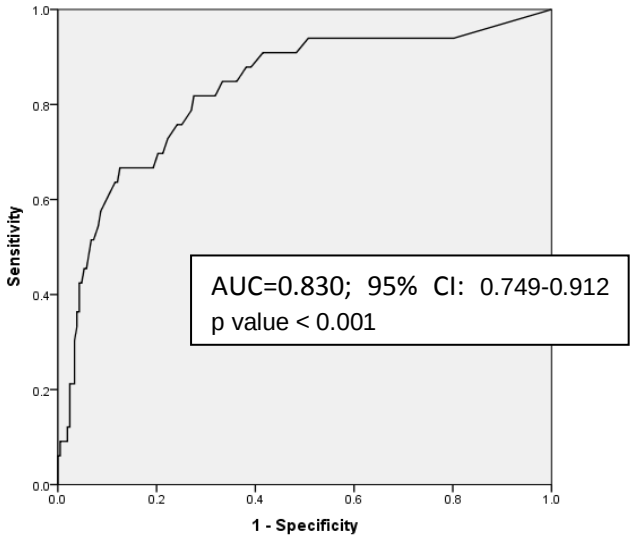
Table 2. Albumin creatinine ratio (ACR) in type 2 DM patients with control group.

ACR	Type 2 DM	Controls	X^2	df	P-value
Normal	87(72.5%)	120(100.0%)	36.261	1	< 0.001
Microalbuminuria	33(27.5%)	0 (0.0%)			
Total	**120 (100.0)**	**120 (100.0)**			

X^2=Chi square; df= degree of freedom

Table 3. Validity test for urinary fibronectin as a marker of early glomerular injury against a fold standard of microalbuminuria among type 2 DM patients.

		Microalbuminuria (Gold standard)		
		Present	**Absent**	**Total**
Urinary Fibronectin (Test: Bio-marker)	**Present**	31 *True positive*	80 *False positive*	111 *Total positive by test*
	Absent	2 *False negative*	7 *True negative*	9 *Total negatives by test*
	Total	33 *Total positive by gold standard*	87 *Total negatives by gold standard*	120 *Total type 2 DM patient*



AUC = Area under the curve; CI= Confidence interval

Figure 1. Receiver Operator Characteristics (ROC) Curve of Urinary Fibronectin as a marker of Glomerular Injury

$$\text{NPV} = \frac{\text{True negative}}{\text{True negative + false negative}} \times \frac{100}{1}$$

$$= \frac{7}{7+2} \times \frac{100}{1}$$

$$= \frac{7}{9} \times \frac{100}{1} = 77.8\%$$

DISCUSSION

Microalbuminuria is a well recognized marker of early glomerular injury in DM patients. The finding in the present study, showing that 27.5% of type 2 DM patients were microalbuminuric is comparable to a similar hospital based study in Northern India (Kanakamani *et al* 2010). However, another hospital based study carried out in Port Harcourt, Nigeria reported that 38 out of the 60 diagnosed type 2 DM patients (63.3%) had microalbuminuria (Orluwene *et al*., 2008). This wide disparity with present study could be attributed to the differences in the eligibility criteria of the study populations. While the study population of present study comprised type 2 DM who were not hypertensive, the previous study did not exclude hypertensive type 2 DM patients. It has been noted that the co-morbid conditions of diabetes and hypertension increase the risk of microalbuminuria (Parchwani *et al*., 2012). Additionally, in the previous study microalbuminuria was determined qualitatively (dipstick) while in the present study microalbuminuria was determined quantitatively. Hence, the possible explanations for the higher rate reported in the later study.

Another study in Jos, Nigeria among newly diagnosed type 2 DM patients reported that 49.2% of these patients had microalbuminuria,(Agba et al., 2004) this finding is also higher than the present study. Noteworthy, a similar study carried out in Enugu, Nigeria reported a much lower rate of 16.1% among type 2 DM patients (Ogbu *et al* 2009., 2009). The reason for this could be due to the smaller study population size in the Enugu study. In spite of their differences in the reporting rates of microalbuminuria among type 2 DM patient, the findings of this present study along with the aforementioned Nigeria studies reveal that microalbuminuria among type 2 DM patients is not uncommon. Thus, highlighting the need for a regular check for microalbuminuria among type 2 DM patients, in order to detect and treat early glomerular damage. It is interesting to note that research has shown that some type 2 DM patients with glomerular damage may not develop microalbuminuria (An *et al*., 2009). There is, therefore, the need for the exploration of other biomarkers for the detection of glomerular damage.

Urinary fibronectin excretion as a marker for the detection of early glomerular damage investigated in the present study revealed findings which are in keeping with current literature (Takahashi 1995; Fagerudd et al., 1997). In agreement with the study by Takahashi (1995), this study showed that the mean urinary fibronectin excretion levels were significantly higher in the diabetic group than the control group.

The study by Takahashi (1995) found that the mean urinary fibronectin excretion level is much higher in type 2 DM with microvascular complications (retinopathy, neuropathy, nephropathy); the level was still higher in those without such complications when compared to controls. This is in agreement with findings in the present study which considered those without complications that the mean urinary fibronectin level is significantly higher in DM than normal controls.

The sensitivity of urinary fibronectin excretion against the gold standard (microalbuminuria) reported in this study (93.9%) highlights the need for its incorporation as a screening tool for glomerular damage. High sensitivity is a necessity for any screening tool as recommended by the World Health Organization (WHO) screening criteria (Andermann *et al*., 2008). Additionally, the significant positive correlation between urinary fibronectin and microalbuminuria reported in this study reflects the good comparison of this biomarker to microalbuminuria. Nonetheless, the low specificity (8.0%) of urinary fibronectin in this study shows that it may be a poor biomarker for the identification of DM subjects as not having a glomerular injury. In other words, it has a reduced ability to correctly classify subjects as not having the diabetic kidney disease. Furthermore, the positive predictive value of 27.9% suggests that the probability of actually having a glomerular injury in a subject with DM who screened positive for fibronectin is low. Therefore, more studies in other centres in Nigeria involving larger samples should be carried out to corroborate the findings of this study. Nonetheless, the high negative predictive value (77.8%) reported indicates its usefulness as a screening tool for the detection of glomerular damage. Moreover, the usefulness of urinary fibronectin as an early marker of diabetic kidney disease in relation to microalbuminuria is buttressed by the relative high area under the curve (AUC) value of 0.830 in the ROC curve.

CONCLUSION

Traditionally, microalbuminuria is used as the gold standard marker for the detection of early diabetic kidney disease in type 2 DM patients. However, it has many pitfalls, including the fact that not every diabetic with diabetic kidney disease will develop microalbuminuria and that it occurs when significant kidney damage had already occurred. The high sensitivity, NPV and AUC value for urinary fibronectin in the detection of diabetic kidney disease in the present study indicates that it

could serve as a useful biomarker in the renal evaluation of type 2 DM patients.

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