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Original Article

Study of Normoalbuminuric Diabetic Nephropathy in Type 1 Diabetics

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Abstract

Introduction: Diabetic kidney disease (DKD) is one of the primary causes of end-stage renal disease. Early diagnosis is very important in preventing the development of DKD. Urinary albumin excretion rate and glomerular filtration rate (GFR) are widely accepted as criteria for the diagnosis and clinical grading of DKD, and microalbuminuria has been recommended as the first clinical sign of DKD.

Aim: The aim of the study was to study the existence of normoalbuminuric diabetic nephropathy in type 1 diabetics

Materials and Methods: This prospective study was conducted in type 1 diabetic by documenting low c-peptide level. Fasting lipid profile was done in these patients. Serum electrolytes such as potassium, sodium, magnesium, and uric acid were measured. The characteristic profile of patients with duration of diabetes and low GFR was analyzed with respect to the duration of diabetes, serum magnesium level, hypertension, retinopathy, and renal biopsy features.

Results: In 95 patients, of 17 patients with renal biopsy-proven normoalbuminuric diabetic nephropathy, 11 patients (65%) had serum magnesium of <2 mg/dl, and only six patients had serum magnesium of >2 mg/dl. Among the 17 patients, five patients (29%) had hypertension and eight patients (47%) had diabetic retinopathy changes.

Conclusion: There exists an entity – normoalbuminuric diabetic nephropathy in type 1 diabetic patients. The incidence of normoalbuminuric diabetic nephropathy increases with duration of diabetes.

Key words: Diabetes, Nephropathy, Normoalbuminuria

INTRODUCTION

Diabetes is the leading cause of end-stage renal disease (ESRD) throughout the world. Diabetic nephropathy occurs in 25–30% of type 1 diabetes. Increased albumin excretion rate has been considered the first clinical sign of diabetic nephropathy both in type1 and types 2 diabetes.[1] Although microalbuminuria is considered as the early marker of diabetic nephropathy, in some patients decrease in glomerular filtration rate (GFR) and hypertension may proceed.[2] It has been proved that patients with normoalbuminuria and decreased GFR in type 2 and type 1 diabetic patients had significant glomerular changes in renal histopathology and also have been proved that these patients had rapid progression of diabetic renal disease.[3] As albuminuria is not a predictor, but a marker of diabetic nephropathy lot of researches had been undertaken to identify early predictors such as hyperfiltration, estimation of early GFR decline with both creatinine and cystatin c, plasma and urinary markers of inflammatory, oxidative pathways, and fibrotic pathways as well as genetic variants that predispose patients to the onset and progression of diabetic nephropathy. Mogensen proposed the natural history of diabetic nephropathy in type1 diabetic patients. Accordingly, Stage 1 is characterized by hyperfiltration and hypertrophy of glomeruli, Stage 2 basement membrane thickening and mesangial expansion, Stage 3 microalbuminuria (incipient nephropathy), Stage 4

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macroalbuminuria and decline in GFR(overt nephropathy), and Stage 5 ESRD.[4] This traditional view of the natural history of diabetic kidney disease (DKD) is now challenged. It is clear that patients spontaneously regress from microalbuminuria and even overt nephropathy levels of proteinuria to normal levels of proteinuria and some patients never develop proteinuria at all before progressing onto decreasing GFR and end-stage kidney disease. Hence, the true value of albuminuria is questioned. The existence of normoalbuminuric DKD was demonstrated in the United Kingdom Prospective Diabetes Study (UKPDS). A landmark study by Perkins and Krolewski showed that in 400 patients in Joslin diabetes center with type 1 diabetes were more likely to regress in their albuminuria than to go on and progress to nephropathy. They followed them for a baseline level of 2 years showing that they had persistent microalbuminuria for those 2 years, and then they followed them for an additional 6 years, and they averaged their albuminuria levels at 2 year intervals. At years 2–4 and 6 about 40% exhibited regression, all spontaneously whereas only 7–15% progressed on to nephropathy. Those who were younger, hemoglobin A1c <8%, systolic blood pressure of <115, and lower total cholesterol and triglycerides were more likely to regress.[5] Hovind *et al.* at the steno diabetes center looked at patients with diabetes and nephrotic range of proteinuria and followed them for an average of 5–6 years and found that among 126 patients 22% remitted spontaneously. They also pointed out that younger patients, those with low mean arterial blood pressure and low serum cholesterol were those who had spontaneous regression There are also reports saying that even typical nodular sclerosis can reverse following strict euglycemia as of following pancreatic transplant for type 1 diabetes in a period of up to 10 years.[6]

Aim

The aim of the study was to study the existence of normoalbuminuric diabetic nephropathy in type 1 diabetics

MATERIALS AND METHODS

In this prospective study, Type 1 diabetic patients attending the Kilpauk Medical College Outpatient Department were enrolled in the study. These patients were confirmed as type 1 diabetic by documenting low c-peptide level. Height, weight, body mass index, and smoking habits were recorded. Time of diagnosis of diabetes was enquired and the presenting symptom at the time of diagnosis was recorded. All these patients were questioned for hospitalization for any illness and comorbid conditions. The requirement for insulin and their compliance with insulin were recorded. These patients were enquired for other drug intake and indigenous medicine intake. Pulse rate, blood pressure, and peripheral pulses were recorded. These patients were assessed for gastropathy, peripheral neuropathy, and autonomic neuropathy. Electrocardiogram and Echocardiography was done for selected patients. They were also examined for diabetic retinopathy by direct ophthalmoscopic evaluation and fluorescein angiography if necessary by the ophthalmologist. Fasting lipid profile was done in these patients. Serum electrolytes such as potassium, sodium, magnesium, and uric acid were measured. These patients were screened for viral markers such as hepatitis B, hepatitis C, and HIV. Ultrasonogram abdomen and a kidney, ureter, and bladder were done and kidney size was assessed. The urine was screened for proteinuria by the sulfosalicylic acid method. Those who were negative for albuminuria were screened for microalbuminuria. Serum creatinine was measured on 2 consecutive days by Jaffe's method and the mean serum creatinine was calculated. GFR was calculated by Cockcroft and Gault formula and those patients with a low GFR (<90 ml/min/1.73 m^2) were identified. We had 37 patients with low GFR and normoalbuminuria (negative for microalbuminuria). These patients with low GFR by Cockcroft and Gault formula and negative for microalbuminuria (37 patients) were screened for GFR by diethylenetriaminepentaacetic acid (DTPA) scan. After doing radionuclide study (DTPA scan), we had 20 patients with normoalbuminuria and negative for microalbuminuria and low GFR (<90 ml/min). These patients were subjected to renal biopsy after getting informed written consent. Renal biopsy was done as an outpatient procedure and we had no complications. Two samples were taken and sent in formalin to renal pathologists for light microscopic studies. Electron microscopic examination was not done due to unavailability. 20 patients with normoalbuminuria and normal GFR (>90 ml/min by DTPA scan) who were age- and sex-matched with those with low GFR were registered as a control. Duration of diabetes, in the normal GFR and low GFR were compared. Serum magnesium level was compared between these two groups. The incidence of hypertension and retinopathy in both these groups was compared. The characteristic profile of patients with low GFR was analyzed with respect to the duration of diabetes, serum magnesium level, hypertension, retinopathy, and renal biopsy features. Statistical methods such as Chi-square and student *t*-test were applied.

RESULTS

A total number of Type 1 diabetic patients screened in this study were 95. Of which we selected 20 patients with normoalbuminuria and low GFR by radionuclide scan. We compared these patients with age- and sex-matched 20 patients with normoalbuminuria and normal GFR (>90 ml/min by DTPA scan). Both of these groups

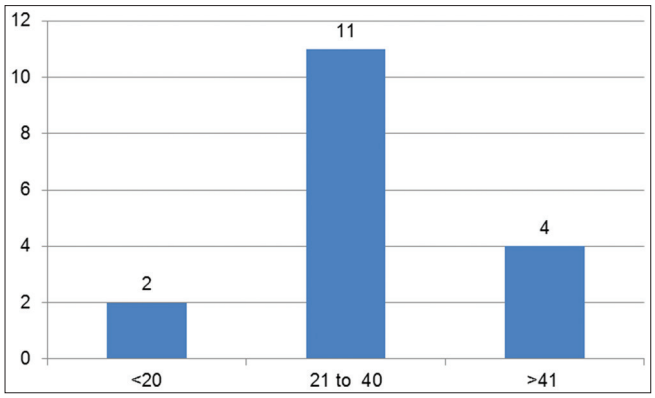

Figure 1: Distribution of age group of normoalbuminuric diabetic nephropathy

Table 1: Cross tabulation of GFR with variables

Characteristics	GFR		*P*-value
	<90 ml	>90 ml	
Hypertension			
Yes	5	1	0.08
No	15	19	
Retinopathy			
Yes	8	1	0.007
No	12	19	

GFR: Glomerular filtration rate

Table 2: Cross tabulation of the duration of diabetes with variables

Characteristics	Duration of diabetes		*P*-value
	<10 years	>10 years	
Hypertension			
Yes	0	5	<0.0001
No	12	3	
Magnesium			
<2	8	5	0.858
>2	4	3	
Retinopathy			
Yes	1	7	<0.0001
No	11	1	
Renal biopsy			
Yes	9	8	0.139
No	3	0	

were sex- and age-matched. The duration of diabetes in patients with low GFR ranges from 5 years to 29 years and among patients with normal GFR it was 3 years–9 years. The mean duration of diabetes in low GFR group was 12 years, and among normal GFR it was 5 years. The GFR in the low GFR group ranges from 25 to 89, and it was in the range of 92–105 in a normal GFR group. The mean GFR in low GFR group was 68, and in the normal GFR group, it was 97. The mean serum magnesium was 1.9 in the low GFR group and it was 2.4 in normal GFR group. Hypertension was seen in five patients (25%) in the low GFR group and it was seen only in one patient (5%) in the normal GFR group. Retinopathy was seen in eight patients (40%) in the low GFR group and only in one patient (5%) in the normal GFR group [Table 1]. Renal biopsy was done in all the 20 patients in low GFR group of which 14 patients showed characteristic diabetic changes of diffuse glomerulosclerosis and no other cause could be ascribed for low GFR, and three patients showed nodular sclerosis along with diffuse changes. Three patients showed an atypical pattern with predominant tubulointerstitial involvement with tubular atrophy, interstitial fibrosis, and arteriolar hyalinosis. We had 17 patients with renal biopsy-proven normoalbuminuric diabetic nephropathy. Of the 17 patients, eight (47%) were male and the age ranges from 19 to 47 years with a mean age of 33 years. Two patients were <20 years of age, and 11 patients were between 20 years and 40 years, and four patients were >40 years [Figure 1]. 13 patients (76%) had GFR of >75 and 4 (24%) patients had GFR of >75. The mean GFR was found to be 67 ml/min. Nine patients had a diabetic duration of fewer than 10 years and eight patients had a duration of >10 years. The mean duration of diabetes in this study group was found to be 11 years. Nine patients had a diabetic duration of fewer than 10 years and eight patients had a duration of >10 years. The mean duration of diabetes in this study group was found to be 11 years. Among the 17 patients, five patients (29%) had hypertension and eight patients (47%) had diabetic retinopathy changes. Among eight patients with duration of diabetes >10 years five had hypertension and seven patients had diabetic retinopathy changes [Table 2].

DISCUSSION

Long-standing Type 1 diabetic patients with normal albumin excretion rate are still at risk of developing clinically significant nephropathy. It is, therefore, important to identify markers of increased nephropathy risk among these patients. One possibility is to perform a kidney biopsy in such patients. However, this is not very practical in most clinical settings. Thus, we examined whether reduced GFR can be predictive of more advanced underlying glomerular lesions. It was first reported that reduced GFR in eight normoalbuminuric longstanding Type 1 diabetic women was associated with worse diabetic glomerular lesions. Shortly thereafter, a small group of 0normoalbuminuric long-standing Type 1 and Type 2 diabetic largely female patients with reduced GFR was described. A similar prevalence of reduced GFR was reported among longstanding normoalbuminuric and normotensive Type1 diabetic patients in Brazil.[7] However, many other investigators did not encounter reduced GFR in normoalbuminuric Type 1 diabetic patients.

The existence of normoalbuminuric DKD was demonstrated in the UKPDS. In this cohort study, they followed 4000 diabetic patients with normoalbuminuria and normal creatinine clearance as estimated by Cockcroft and Gault formula. They followed them for a median of about 15 years. In this, about 12% of patients with microalbuminuria manifested with a decreased creatinine clearance first. Of those patients with decreased creatinine clearance, about 51% never had albuminuria at all.[8,9] In our study, we analyzed 95 Type 1 diabetic patients. 45 were female and 50 were male. Most of them were in the age group of 20–40 years with a mean duration of <10 years in 60 patients and >10 years in 35 patients. In this study, the mean GFR was low in female compared to male and in those patients with long duration of diabetes (>10 years). In this study, we compared the 20 patients with low GFR and 20 patients with normal GFR. The sample size is small as we did this study in Type 1 diabetic patients. There was no significant sex and age difference between these two groups as the patient selection was done by matching these parameters. The mean GFR was found to be 68 ml/min in low GFR group and it was 97 ml/min in the normal GFR group. The duration of diabetes in the low GFR group is 12 years and it is 5 years in normal GFR group. This data are highly significant and this emphasizes the fact that the incidence of normoalbuminuric diabetic nephropathy increases as the duration of diabetes increases. This is the same as we see in albuminuric diabetic nephropathy. The mean serum magnesium is 1.9 in patients with low GFR and it is 2.4 in normal for group. This is statistically significant. Many studies are showing that lower magnesium level in diabetic patients is associated with increased incidence of comorbid illness.[10] If this is proved right then, these patients with low GFR are more prone to diabetic end-organ complications. Hypertension is seen in five patients with low GFR while it is seen in only one patient with normal GFR. Similarly, retinopathy is seen in eight patients with low GFR while it is seen in only one patient with normal GFR. These data are statistically significant. This confirms the fact that these patients with low GFR are placed in a high-risk zone comparing to those with normal GFR. In general, there is heterogeneity in the renal biopsy in diabetics. There are three categories identified: Category 1 normal or near normal structure, just a mild amount of mesangial expansion, Category 2 thickening of basement membrane, arteriolar hyalinosis, and nodular mesangial expansion, and Category 3 atypical patterns of renal injury with a more tubulointerstitial disease where the tubular basement membrane was thickened and that there were more tubular atrophy, a lot more interstitial fibrosis, and much greater arteriolar hyalinosis.[11] In a study by nosadini, they looked at a large cohort of patients in Italy. They followed them from the initial diagnosis of diabetes until they got to a GFR estimated with a creatinine of about 60–75. Then, they made sure that that was actually their GFR measuring it with isotope-labeled creatinine ethylenediaminetetraacetic acid. They found that 30 of these patients had albuminuria and 27, again, had normal albuminuria. Then they went on to biopsy them. Interestingly, 93% of the patients who had albuminuria had the typical diabetic histopathology whereas only about 20% with normal albuminuria had this pathology. It was more often those with normal albuminuria who fell into Category 3. Very few of those with albuminuria exhibited this category. Hence, they assumed that it is the difference in histology that accounts for this existence of normoalbuminuric DKD and that, in fact, this may be reflective of more the vascular outcomes in diabetes rather than the specific glomerular diabetic nephropathy that we always assume patients to have.[12] In this study, we did a renal biopsy to those 20 patients with low GFR, and we found that 17 patients had typical diabetic nephropathy changes. Only three patients we had the histology showing predominant tubulointerstitial changes. Hence, we have this data paradoxical to this Italian study. When we analyzed the 17 patients with typical diabetic nephropathy changes, we could not find any statistically significant change with respect to gender. Among them, 13 patients had GFR l<75ml/min. As we had five patients with hypertension among these 17 patients, the incidence of hypertension among these normoalbuminuric diabetic nephropathy from our study is 35%. Similarly, we had eight patients with retinopathy in this group accounting for an incidence of 48%. Hence, there is an increased incidence of hypertension and retinopathy in this normoalbuminuric diabetic nephropathy population.

CONCLUSION

There exists an entity – normoalbuminuric diabetic nephropathy in Type 1 diabetic patients. The incidence of normoalbuminuric diabetic nephropathy increases with duration of diabetes. There is an increased incidence of hypertension (29%) and retinopathy (47%) in this group of patients. Serum magnesium is low in these patients with normoalbuminuric diabetic nephropathy the significance of which is not clearly known; yet, there are studies to say that low magnesium is associated with poor outcome. Hence, along with screening for albuminuria periodic screening for GFR should also be done so that this normoalbuminuric diabetic nephropathy can be detected early. This patient should be treated as high risk and they should avoid radiocontrast and other nephrotoxic drugs if not mandatory.

REFERENCES

1. Mogensen CE. Microalbuminuria, blood pressure and diabetic renal disease: Origin and development of ideas. Diabetologia 1999;42:263-85.

2. Lane PH, Steffes MW, Mauer SM. Glomerular structure in IDDM women with low glomerular filtration rate and normalalbumin excretion. Diabetes 1992; 41:581-6.
3. Caramori ML, Fioretto P, Mauer M. Low glomerular filtration rate in normoalbuminuric Type 1 diabetic patients: An indicator of more advanced glomerular lesions. Diabetes 2003;52:1036-40.
4. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease: With emphasis on the stage of incipient diabetic nephropathy. Diabetes 1983;32 Suppl 2:64.
5. Perkins BA, Krolewski AS. Early nephropathy in Type 1 diabetes: A new perspective on who will and who will not progress. Curr Diab Rep 2005;5:455-63.
6. Hovind P, Tarnow L, Rossing K, Rossing P, Eising S, Larsen N, *et al*. Decreasing incidence of severe diabetic microan-giopathy in Type 1 diabetes. Diabetes Care 2003;26:1258.
7. Caramori ML, Gross JL, Pecis M, de Azevedo MJ. Glomerular filtration rate, urinary albumin excretion rate, and blood pressure changes in normoalbuminuric normotensive Type 1 diabetic patients: An 8-year follow-up study. Diabetes Care 1999;22:1512-6.
8. Retnakaran R, Cull CA, Thorne KI, Adler AI, Holman RR, UKPDS Study Group. Risk factors for renal dysfunction in Type 2 diabetes: U.K. Prospective diabetes study 74. Diabetes 2006;55:1832-9.
9. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, *et al*. Development and progression of nephropathy in Type 2 diabetes: The United Kingdom prospective diabetes study (UKPDS 64). Kidney Int 2003; 63:225-32.
10. Pham PC, Pham PM, Pham PA, Pham SV, Pham HV, Miller JM, *et al*. Lower serum magnesium levels are associated with more rapid decline of renal function in patients with diabetes mellitus Type 2. Clin Nephrol 2005; 63:429-36.
11. Fioretto P, Caramori ML, Mauer M. The kidney in diabetes: Dynamic pathways of injury and repair. The Camillo Golgi lecture 2007. Diabetologia 2008; 51:1347-55.
12. Nosadini R, Velussi M, Brocco E, Abaterusso C, Carraro A, Piarulli F, *et al*. Increased renal arterial resistance predicts the course of renal function in Type 2 diabetes with microalbuminuria. Diabetes 2005;55:234-9.

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