Original Research Article

Study of early diagnosis of diabetic nephropathy using spot urine microalbumin in type 2 diabetes mellitus patients at a tertiary care center

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Abstract

Background: Diabetic nephropathy is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. Detection of microalbuminuria is the most important screening tool for early phase of diabetic renal disease called incipient diabetic nephropathy. Present study was designed to study role of spot urine microalbumin for early diagnosis of diabetic nephropathy in type 2 diabetes mellitus patients. **Material and Methods:** Present study was cross-sectional, prospective, observational study conducted in outpatient department of medicine in recently diagnosed (less than six months duration) type-2 diabetes mellitus patients, negative for albumin in urine by dipstic method. Micral test was used for estimation of microalbuminuria. eGFR (estimation of glomerular filtration rate), calculated by the Modification of Diet in Renal Disease (MDRD) equation. **Results:** After applying inclusion and exclusion criteria, total 280 patients were included in present study. 180 patients had negative micral test, rest 100 with positive micral test were evaluated further. Micro-albuminuria was increasing with increasing levels of HbA1c. All patients with ≥10.0 levels of HbA1c had severe micro-albuminuria. eGFR levels are decreasing with increasing levels of microalbuminuria. We noted 65, 22, 13 patients had eGFR(ml/min/1.73 m2). **Conclusion:** Early diagnosis of diabetic nephropathy can be effectively done using spot urine microalbumin in type 2 diabetes mellitus patients.

Key Words: diabetic nephropathy, urine microalbumin, type 2 diabetes mellitus

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic, widely prevalent endocrine disease, which is characterized by hyperglycemia due to defects in insulin secretion, insulin action or both[1]. Diabetic patients are at an increased risk of developing specific complications including nephropathy, retinopathy neuropathy and atherosclerosis. Diabetic nephropathy occurs in approximately one third type 2 diabetes[2]. DM is the major cause of renal morbidity and mortality, and diabetic nephropathy is one of chronic kidney failure, accounting for nearly 44 percent of new cases[3]. Globally, it is estimated that 415 million people had diabetes in 2015 which is expected to reach 642 million by 20404. This global pandemic principally involves type 2 diabetes mellitus. Diabetic nephropathy also called as Kimmelsteil Wilson syndrome is characterized by a progressive increase in the excretion of protein particularly albumin, an early and continuing rise in blood pressure and a late decline in glomerular filtration rate (GFR) resulting in end stage renal disease.

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If protein is detectable on a standard dipstick suggestive of macroalbuminuria >300 mg/day. Microalbuminuria is defined as urinary excretion of 30- 300 mg/day of albumin. Detection of microalbuminuria is the most important screening tool for early phase of diabetic renal disease called incipient diabetic nephropathy. Generally at this stage urine is negative for standard dipstick test and must be screened by the use of sensitive tests. Diabetic nephropathy is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases. It is categorized into two stages: microalbuminuria (UAE ≥ 20 microg/min and ≤ 199microg/min) and macroalbuminuria (UAE≥200 microg/ min)5. Early diagnosis and treatment delays or prevents the onset of diabetic nephropathy and progression of diabetic kidney disease. Present study was designed to study role of spot urine microalbumin for early diagnosis of diabetic nephropathy in type 2 diabetes mellitus patients.

MATERIAL AND METHODS

Present study was cross-sectional, prospective, observational study conducted in outpatient Department of Biochemistry, Shri Shankaracharya Institute of Medical Sciences, Junwani, Bhilai. Study was carried out between Sept 2018 to August 2019. Study was approved by the institutional ethics committee and written informed consent was taken from all the patients.

Inclusion criteria - recently diagnosed (less than six months duration) type-2 diabetes mellitus patients, negative for albumin in urine by dipstic method.

Exclusion criteria - patients with overt albuminuria (>350 mg/ day), congestive cardiac failure, urinary tract infection, pregnant patients, patients confined to bed for more than two weeks, and patients on ACE inhibitors for hypertension.

The selected patients were studied in detail with history and physical examination, including detailed neurological examination. Patients underwent investigations such as serum creatinine and HbA1c. In the present study, micral test was used for estimation of microalbuminuria. The micral test is a test-strip method in which the color reaction is mediated by an antibody-bound enzyme. This method has shown good correlations with radioimmunoassay and can be readily used for screening. Spot estimation of microalbuminuria was carried. Test strip was immersed in urine such that the fluid level was between two black bars. Strip was withdrawn after five seconds. Strip was placed horizontally across the urine vessel and the color change in test zone was compared with color scale after one minute. Microalbuminuria was graded as mild (20–50 mg/L), moderate (50–100 mg/L), or severe (100–300 mg/L) depending on the color change in the strip. eGFR (estimation of glomerular filtration rate) (in millilitres per min per 1.73 m2), calculated by the Modification of Diet in Renal Disease (MDRD)6 equation in patients. MDRD (Modification of Diet in Renal Disease) derived eGFR calculated using the formula as follows: eGFR = 186 × (SCR × 0.011)-1.154 × (age)-0.203 × (0.742, if female) × (1.210 if African American) (SCR- serum creatinine expressed as µmol/L). Data was collected in excel sheet and analysed.

RESULTS

After applying inclusion and exclusion criteria, total 280 patients were included in present study. 180 patients had negative micral test, rest 100 with positive micral test were evaluated further.

Table 1: Quantitative analysis of microalbuminuria in study patients

Microalbuminuria (mg/l)	No. of patients	Percentage
Mild (20mg/l)	59	59
Moderate (50mg/l)	24	24
Severe (100mg/l)	17	17
Total	**100**	**100**

In patients with positive micral test, HbA1c was analysed. Micro-albuminuria was increasing with increasing levels of HbA1c. All patients with ≥10.0 levels of HbA1c had severe micro-albuminuria,

Table 2: Correlation of albuminuria with HbA1c in study subjects

Microalbuminuria (mg/l)	<7	7.0-7.9	8.0-9.9	≥10.0	
Mild (20mg/l)	49	9	1	0	59
Moderate (50mg/l)	4	12	8	0	24
Severe (100mg/l)	0	3	6	8	17
Total	**53**	**24**	**15**	**8**	**100**

Similarly we compared estimated GFR (eGFR) with levels of micro-albuminuria. eGFR levels are decresing with increasing levels of microalbuminuria. We noted 65, 22, 13 patients had eGFR(ml/min/1.73 m2).

Table 3: Correlation of albuminuria with eGFR in study subjects

Microalbuminuria (mg/l)	eGFR (ml/min/1.73 m2)			Total
	>90	60-89	30-59	
Mild (20mg/l)	58	59	1	0
Moderate (50mg/l)	5	24	12	7
Severe (100mg/l)	2	17	9	6
Total	**65**	**100**	**22**	**13**

DISCUSSION

Microalbuminuria has also emerged as an important risk factor for left ventricular hypertrophy, myocardial infarction, stroke, peripheral vascular diseases and retinopathy, independent of blood pressure. Strong evidence exists that improved glycemic control is effective at lessening the risks of nephropathy, retinopathy and neuropathy in diabetes[7]. A clinically asymptomatic point of failure follows with development of microalbuminuria (30 mg albumin per day) to macroalbuminuria (>300 mg albumin per day). Once overt nephropathy (macroalbuminuria) has established, renal function falls at a significant but alterable rate (decline in GFR of 220 ml/min/ year). The rate of decline depends on type of diabetes, genetic predisposition, glycaemic control and, very significantly, blood pressure[8]. Natural clinical course of diabetic nephropathy can be divided into five stages as follows[9].

Stage 1: Renal pathology develops at the onset of diabetes. By the time of diagnosis, the GFR and urinary albumin excretion (UAE) have been increased. It can be controlled at this level by onset of insulin.

Stage 2: The second phase typically lasts for 5-15 years after diagnosis of diabetes. GFR remains elevated due to hyperfiltration. Kidneys remain hypertrophied and UAE rate stays normal.

Stage 3: The characteristics of stage three are:

1. Microalbuminuria is present. It occurs in 30-50% of patients after diabetes onset, 80% of whom go on to develop overt nephropathy over 10-15 years.
2. GFR remains elevated or returns to normal range
3. Blood pressure starts to rise in 60% of patients

Stage 4: This stage is also known as clinical nephropathy or overt nephropathy. The characteristic histological features of stage four are formation of the Kimmelstiel-Wilson nodule (focal glomerular sclerosis) and macroproteinuria. It can progress to nephrotic in 30% of patients or may decline in 80% depending on deterioration of GFR.

Stage 5: As the GFR continues to decline, ESRD may develop. DN is considered the most common cause of ESRD because of associated autoimmune neuropathy and cardiac disease.

Annual screening of all individuals with diabetes is recommended to detect abnormal and/or changing levels of albuminuria and renal function (i.e., eGFR), so that early renoprotective treatment may be initiated10. Renal function has been graded according to the Kidney Disease Outcomes Quality Initiative guidelines as stages of diabetic nephropathy[11,12].

Table 4: Stages of diabetic nephropathy

Stage	GFR (ml/min/1.73 m2)	Description	Management
1	>90	Normal or increased GFR with another evidence of renal damage	Screening CKD and risk reduction
2	60-89	Slightly decreased GFR with another evidence of renal damage	Diagnosis and treatment: slow progression of CKD; comorbidities and cardiovascular disease; risk reduction
3a	45-59	Moderately decreased GFR without evidence of renal damage	Evaluate and treat complication
3b	30-44	Irreversible renal damage	
4	15-29	Severely decreased GFR without evidence of renal damage	Prepare for renal replacement therapy
5	<15	Established renal failure	Renal replacement if uremic

Improved glycemic control has been demonstrated to reduce micro and macro vascular complications in patients with diabetes. Glycated hemoglobin (HbA1c) is the preferred and widely utilized biomarker of glycemic control in subjects with diabetes with higher concentrations of glucose[13]. In a study on newly diagnosed T2DM patients HbA1c concentrations were reported to be significantly higher in the microalbuminuria group compared with the normoalbuminuric patients ($p<0.001$). The authors also observed that HbA1c value above 8% was associated with higher incidence (44%) of microalbuminuria[14]. We

noted similar findings in present study. Albuminuria within the microalbuminuric range has been shown to be associated with an increased risk for the development of end-stage kidney disease (ESKD) compared with normoalbuminuria, in a meta-analysis of eight studies with an overall relative risk for ESKD of 4.8 (95% confidence interval (CI): 3–7.5)[15]. In a similar manner, a meta-analysis of five studies involving subjects with type 2 diabetes found that microalbuminuria was associated with a relative risk of 3.6 (95% CI: 1.6–8.4) for the development of ESKD compared with normoalbuminuria[16]. We also noted decreasing value of eGFR with increasing levels of microalbuminuria. Early-morning spot urine collections are sufficient for screening and monitoring, and are convenient for the patient[17,18]. Simultaneous measurement of spot urine albumin and creatinine values, which allows normalization of these values, is helpful to overcome the variability in urine concentrations caused by hydration and is accepted widely as the marker for the screening of albuminuria[19]. American Diabetes Association position statement (2012) recommendations for nephropathy screening advises estimation of urinary albumin annually in patients with type 1 diabetes of duration of ≥5 years and type 2 diabetic patients at diagnosis; it also recommends estimation of serum creatinine annually in all adult diabetic patients to evaluate renal functions[20].

CONCLUSION

Early diagnosis of diabetic nephropathy can be effectively done using spot urine microalbumin in type 2 diabetes mellitus patients. Before estimation of urine microalbumin, important common causes other than diabetes (eg. Urinary tract infection) of microalbuminuria should be ruled out.

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