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Clinical Utility of Urinary β2 Microglobulin in Detection of Early Nephropathy in type 2 Diabetes Mellitus Patients

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Abstract **Original Research Article**

Background: Diabetic nephropathy is a kidney disease associated with long-standing hyperglycemia. The main features of diabetic nephropathy include nephrotic syndrome with excessive filtration of protein into the urine (proteinuria), high blood pressure (hypertension), and progressive impairment of kidney function. ***Objective:*** To find out the clinical utility of urinary β2 microglobulin in the detection of early nephropathy in type 2 diabetes mellitus patients. ***Methods:*** This cross-sectional study was conducted in the Department of Nephrology, Dhaka Medical College Hospital, over a period of one year from January 2017 to December 2017. 50 type 2 diabetes mellitus patients as the case group and age sex-matched 50 healthy participants as the control group was included in this study as the study population. Socio-demographic, family history, history of patients, and epidemiological data were recorded. A clinical examination investigation was done for all the study population. The urinary β2 microglobulin (β2m) level was assayed using the beta- 2- macroglobulin ELISA kit, EIA 3609. Statistical analysis was done by the Statistical Package for Social Science (SPSS-22). The confidence interval was considered at the 95% level. The sensitivity and specificity of urinary β2m were calculated in detecting early DN. P-value <0.05 was considered statistically significant. ***Result:*** Mean age of the case group was 50.08±12.06 years and the control group was 46.54±9.89 years. Female was predominant in both case and control group. Hypertension, anemia, diabetic nephropathy, and diabetic peripheral neuropathy were found in 24(48%), 17(34%0, 14(28%), and 11(22%) cases. Urinary ACR was found significantly higher in the case group than that of the control group (183.32±164.11 mg/gm vs 13.60±4.40 mg/gm). Similarly, urinary β2 microglobulin was found significantly higher in the case group than in the control group (0.50±0.22 µgm/ml vs 0.14±0.05 µgm/ml). Among early nephropathy patients elevated urinary β2 microglobulin was found in 7(46.7%) cases. Urinary β2 microglobulin in the diagnosis of early nephropathy in diabetic patients showed accuracy, sensitivity, specificity PPV, and NPV were 0.840, 0.971, 0.533, 0.892, and 0.886 respectively. ***Conclusion:*** Urinary β2 microglobulin is a useful marker in the diagnosis of early nephropathy in type 2 diabetes mellitus patients.

Keywords: Urinary β2 microglobulin, Nephropathy, Type 2 Diabetes Mellitus.

INTRODUCTION

Diabetic nephropathy is a severe complication occurring in type 2 diabetic patients and it is associated with an increased risk of all-cause mortality, cardiovascular disease, and progression to end-stage renal disease (ESRD), which requires costly renal replacement therapy of dialysis or transplantation [1, 2]. The early stages cause an elevated glomerular filtration rate with enlarged kidneys, and then the principal feature of diabetic nephropathy is proteinuria. A diagnostic marker to detect DN at an early stage is important as early intervention can slow the loss of kidney function and reduce adverse outcomes. The

appearance of a small amount of protein albumin in urine, called microalbuminuria has been accepted as the earliest marker for the development of DN. However, it has been reported that a large proportion of renal impairment occurs even before the appearance of microalbuminuria [3]. Furthermore, it has been reported to occur in the urine of non-diabetic subjects, indicating the non-specificity of albuminuria for accurate prediction of diabetic kidney disorder [4]. For optimal clinical management of diabetic patients, additional urinary biomarkers that predict DN at a very early stage, even before the appearance of microalbuminuria are needed. Several glomerular and tubular biomarkers predicting the onset or progression of nephropathy in patients with diabetes have been identified and are becoming increasingly important in clinical diagnostics. Recent studies have demonstrated that urinary biomarkers were significantly elevated in normoalbuminuric type 2 diabetic patients compared with nondiabetic control subjects and could be used as markers for earlier, specific and accurate prediction of DN [5, 6]. The interest in the use of biomarkers for early DN derives from the observation that patients with type 2 diabetes pass through a period of pre-diabetes and may experience renal impairment at the time of diagnosis. Although microalbuminuria has been considered the earliest marker of DN in clinical practice, 29.1-61.6 % of individuals with type 2 diabetes could have renal impairment even before the onset of microalbuminuria, the gold standard for early diagnosis [7, 8]. According to a study, type 2 diabetics with normoalbuminuric renal insufficiency were less likely to be identified. As having any impaired kidney function as well as to have had their choice of drug type/ dose-adjusted compared to those with albuminuric renal insufficiency [9]. Thus, aiming to delay its progression and improve outcomes it is necessary to implement different strategies for detecting early DN in patients with diabetes. Before the onset of significant albuminuria and may be used as an early marker of renal injury in DN, increased levels of urinary biomarkers can be detected in diabetic patients. This would play a significant role in the effective management and treatment approaches in diabetic care. The aim of this review is to summarize some new and important urinary biomarkers associated with the early onset of DN and its progression in type 2 diabetic patients. The incidence of diabetic nephropathy is associated with the increasing prevalence of diabetes mellitus [10]. The clinical evaluation of renal function in diabetics involved the use of serum creatinine. For many years various estimations of the glomerular filtration rate using creatinine-based formulae. It has accuracy limitations as it will only detect more advanced cases of diabetic nephropathy. The other methods for the assessment of GFR are either too unwieldy or too expensive to be used. Attention has been focused on the use of persistent microalbuminuria to define the presence of incipient diabetic nephropathy more recently [11]. Though the glomerular origin of microalbuminuria has not been contested, studies in rodents and man have shown that impaired tubular reabsorption of albumin at the proximal convoluted tubule is partly responsible for microalbuminuria [12]. The foregoing suggests that investigations targeting the tubular function in diabetics may be of immense clinical benefit in detecting early diabetic nephropathy, possibly earlier than the occurrence of persistent microalbuminuria. B2-microglobulin is a single-chain, low molecular weight polypeptide [13] and has a similar structure to the CH_3 domain of the immunoglobulin molecule [14]. β2-microglobulin forms the invariant light chain portion of major histocompatibility complex (MHC) class I molecules [15], which can be found on the membrane of all nucleated cells [16]. Thus, cellular membrane turnover is the main source of serum β2-microglobulin [14] Because of its small size, β2-microglobulin is filtered freely through the glomeruli of the kidney. Then, a majority of β2-microglobulin in the filtrate is reabsorbed and catabolized by renal proximal tubular cells [17]. Only trace amounts of β2-microglobulin remain in urine and are excreted [18]. Therefore, β2-microglobulin serves as a useful biomarker to evaluate both glomerular and tubular function [19]. Measurement of urinary β2-microglobulin has emerged as a popular method of assessing tubular function clinically. The aim of this study is to investigate the clinical utility of urinary β2-microglobulin levels in detecting early nephropathy in diabetic patients.

OBJECTIVES

General objective

To find out the clinical utility of Urinary β_2 Mocroglobulin in the detection of early nephropathy in type 2 diabetes mellitus patients.

Specific objectives

- To find out the Urinary β2 microglobulin level in type 2 diabetes mellitus patients
- To find out the Urinary β2 microglobulin level in healthy controls
- To see the correlation of Urinary β2 microglobulin with urinary ACR in type 2 diabetes mellitus patients

MATERIALS & METHOD

It was a cross-sectional study conducted in the Department of Nephrology, Dhaka Medical College Hospital, and Dhaka from January 2017 to December 2017. A total of 49 types 2 diabetes mellitus patients indoor and outdoor at Dhaka Medical College hospital.

The purposive sampling technique was used as per inclusion and exclusion criteria.

Inclusion criteria

- Patients with type 2 diabetes mellitus.
- Adult patients of both sexes
- Patients who gave consent.

Exclusion criteria

- End-stage kidney disease
- H/O urinary tract infection in the one month preceding the interview
- Renal ultrasound suggestive of structural urinary tract abnormalities
- Systemic diseases like SLE, vasculitis, Multiple Myeloma
- Hypertensive patient treated with ACEI/ARB/Cilnidipine/ Spironolactone

All the patients were recruited as per inclusion and exclusion criteria. Sociodemographic, family history, history of patients, and epidemiological data were recorded. A thorough clinical examination was performed for all patients, including vital signs and anthropometric measurements (weight and height), chest examination, heart examination, abdominal examination, and CNS examination. Investigations (urine R/M/E, urinary ACR, S. creatinine, glycated hemoglobin, RBS, and ultrasonogram of KUB) were done. The urinary β_2-microglobulin (β_2m) level in the participants was assayed using the beta-2-microglobulin ELISA kit, EIA 3609, from DRG Diagnostics International Inc., USA, which has a precision of 0.1 µg/mL. A questionnaire was prepared considering key variables like demographic data, clinical presentation, clinical findings, predisposing factors, and investigations were collected. Informed consent was taken from each patient. Statistical analysis of the study was done by the SPSS version 22.0. The result was presented in tables. Data were presented as frequency & percentage and numerical data as mean & standard deviation. The confidence interval was considered at a 95% level. The sensitivity and specificity of urinary β2m were calculated in detecting early DN. P-value<0.05 was considered statistically significant. Ethical clearance was taken from the "Ethical Committee" of DMCH, Dhaka.

RESULTS

Table-I: Distribution of study subjects according to age in case and control (N=100)

Age (years)	Group		P-value
	Case	Control	
≤40 yrs.	13 (26.0)	14 (28.0)	
41-50 yrs.	12 (24.0)	19 (38.0)	
51-60 yrs.	13 (26.0)	9 (18.0)	
>60 yrs.	12 (24.0)	8 (16.0)	
Mean ± SD	50.08 ± 12.06	46.54 ± 9.89	0.112

Table I showed the distribution of study subjects according to age in case and control. The mean age of the cases was 50.08 ± 12.06 years and the control was 46.54 ± 9.89 years. There was no significant difference in age between the case and control.

Table-II: Distribution of study subjects according to gender in case and control (N=100)

Gender	Group		P-value
	Case	Control	
Male	16 (32.0)	21 (42.0)	0.300
Female	34 (68.0)	29 (58.0)	
Male: Female	1:2.12	1:1.38	

Table II showed the distribution of study subjects according to gender in case and control. Females were predominant in both case and control groups. There was no significant difference in age between the case and control groups.

Table-III: Clinical history of diabetes mellitus patients (n=50)

Clinical history	Frequency (n)	Percentage (%)
Burning sensation in limbs	11	22.0
Decreased visual acuity	12	24.0
Numbness of hands and feet	11	22.0
Hypertension	24	48.0
Family history of DM	44	88.0
Family history of HTN	12	24.0
Anti-hypertensive drug	24	48.0
Anti-diabetic drug	50	100.0

Table III showed the clinical history of diabetes mellitus patients. Burning sensation in limbs was observed in 11 (22.0%) cases, decreased visual acuity was found in 12 (24.0%) cases, numbness of hands and feet was found in 11 (22.0%) cases, and hypertension was found in 24 (48.0%) cases. Family history of DM and HTN was found in 44 (88.0%) cases and 12 (24.0%) cases respectively. All patients used to take the anti-diabetic drug and 24 (48.0%) patients have taken the anti-hypertensive drug.

Table-IV: Clinical signs of diabetic Mellitus patients (n=50)

Clinical sign	Mean ± SD	Min-Max
Duration of DM (years)	6.92 ± 4.89	1.00 - 16.00
BMI (kg/m^2)	25.34 ± 3.17	20.00 - 32.00
Pulse (per minute)	84.80 ± 6.48	64.00 - 92.00
Systolic PB (mm of Hg)	120.10 ± 15.53	90.00 - 140.00
Diastolic BP (mm of Hg)	73.60 ± 9.80	60.00 - 95.00
Anemia	17	34.0
Diabetic retinopathy	14	28.0
Diabetic peripheral neuropathy	11	22.0

Table IV showed clinical signs of diabetic patients. The mean duration of DM, BMI, pulse, systolic BP, and diastolic BP were 6.92±4.89 years, 25.34 ± 3.17 kg/m^2, 84.80 ± 6.48 per minute, 120.10 ± 15.53 mm of Hg and 73.60 ± 9.80 mm of Hg respectively. Anemia, diabetic nephropathy, and diabetic peripheral neuropathy were found in 17(34.0%) cases, 14 (28.0%) cases, and 11(22.0%) cases respectively.

Table-V: Clinical signs of diabetes mellitus patients among different nephropathy stages (n=50)

Clinical sign	Stage 1 & 2	Stage 3	Stage 4	p-value
Hypertension	3 (20.0)	10 (45.5)	11 (84.6)	0.001
Anemia	1 (6.7)	5 (22.7)	11 (84.6)	
Diabetic retinopathy	2 (13.3)	2 (9.1)	10 (76.9)	
Diabetic peripheral neuropathy	1 (6.7)	1 (4.5)	9 (69.2)	

Table IV showed clinical signs of diabetic patients among different nephropathy stages.

Table-VI: Laboratory findings of the diabetic Mellitus patients (n=50)

Laboratory parameters	Mean ± SD	Min-Max
RBS (mmol/L)	12.44 ± 6.09	0.50 – 30.00
HbA1c (%)	8.05 ± 2.15	4.90 – 15.00
Serum creatinine (mg/dl)	1.26 ± 0.56	0.45 – 2.70
ACR (mg/gm)	183.32 ± 164.11	9.19 - 481.08
Urinary β2 micro globulin (µgm/ml)	0.50 ± 0.22	0.11 - 1.43
Urinary protein		
Trace	6	12.0
+	22	44.0
++	4	8.0

Table VI showed laboratory findings of diabetic patients. Mean RBS, HbA1c, serum creatinine, urinary ACR and urinary β2 micro globulin were 612.44 ± 6.09 mmol/L, 8.05 ± 2.15 %, 1.26 ± 0.56

mg/dl, 183.32 ± 164.11 mg/gm and 0.50 ± 0.22 µgm/ml respectively. Urinary protein was traced in 6 (12.0%) cases, (+) in 22 (44.0%) cases and (++) in 4 (8.0%) cases.

Table-VII: Laboratory findings of the diabetic Mellitus patients among different nephropathy stages (n=50)

Clinical sign	Stage 1 & 2	Stage 3	Stage 4	P-value
Urinary ACR (mg/gm)	16.68 ± 5.53	158.46±82.71	417.66±51.33	<0.001
Urinary β2 micro globulin (µgm/ml)	0.32 ± 0.20	0.55 ± 0.12	0.63 ± 0.26	

Table VII showed laboratory findings of the diabetic Mellitus patients among different nephropathy stages.

Table-VIII: Urinary ACR and Urinary β2 microglobulin level in case and control (N=100)

	Group		P-value
	Case	Control	
Urinary ACR (mg/gm)	183.32 ± 164.11	13.60 ± 4.40	<0.001
Urinary β2 micro globulin (µgm/ml)	0.50 ± 0.22	0.14 ± 0.05	

Table VIII showed urinary ACR and Urinary β2 microglobulin levels in case and control. Urinary ACR was found significantly higher in the case than that of control (183.32±164.11 mg/gm vs 13.60±4.40 mg/gm). Similarly, Urinary β2 microglobulin was found significantly higher in the case than that of control (0.50±0.22 µgm/ml vs 0.14±0.05 µgm/ml).

Table-IX: Raised urinary β2 microglobulin in Case and Control Group (n=50)

Urinary β2 microglobulin	Group		P-value
	Case	Control	
≥0.3	41(82.0)	2(4.0)	<0.001
<0.3	9(18.0)	48(96.0)	

Table IX showed raised urinary β2 microglobulin in case and control. Raised urinary β2 microglobulin was found in 41 (82.0%) cases and 2 (4.0%) in controls. Raised urinary β2 microglobulin was significantly higher in the case than control groups.

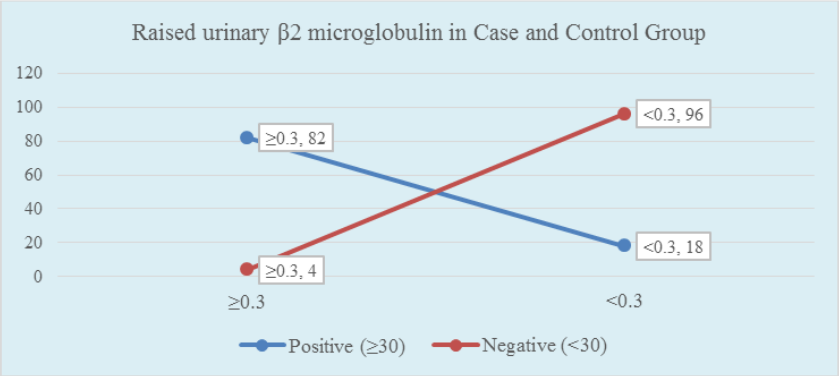

Fig-1: Raised urinary β2 microglobulin in Case and Control Group (N=100)

Table-X: Raised ACR in case and control Group (N=100)

Urinary ACR	Group		P-value
	Case	Control	
≥ 30	35(70.0)	3(6.0)	<0.001
< 30	15(30.0)	47(94.0)	

Table X showed raised urinary ACR in case and control. Raised urinary was found in 35 (70.0%) cases and 3 (6.0%) in controls. Raised ACR was significantly higher in the case than control groups.

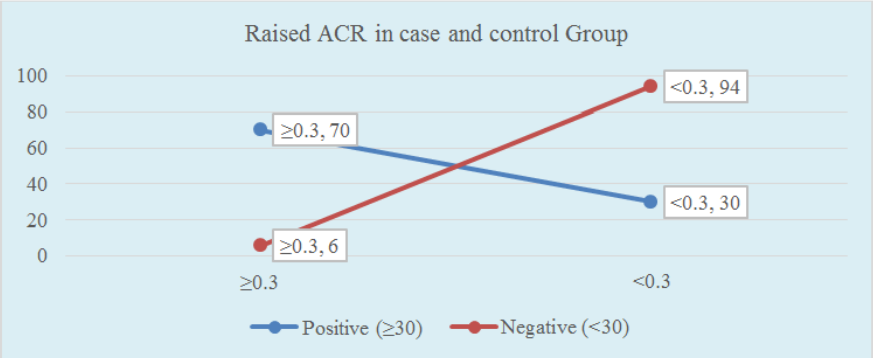

Fig-2: Raised ACR in case and control Group (N=100)

Table-XI: Comparison of urinary β2m and ACR in detecting early DN (n=50)

Urinary β2 microglobulin	ACR		Total
	Positive (≥30)	Negative (<30)	
≥0.3	34(97.1)	7(46.7)	41(82.0)
<0.3	1(2.9)	8(53.3)	9(18.0)

Table XI showed a comparison of urinary β2m and ACR in detecting early DN. Among early nephropathy patients diagnosed with ACR, 7 (46.7%) already had elevated urinary β2 microglobulin. Among the subjects with normal urinary β 2m, only 1(2.9%) had nephropathy.

Table-XII: Validity parameters of urinary β2m in detecting early DN (n=50)

Parameters	Value	Low 95% CI	High 95% CI
Kappa	0.850		
Accuracy	0.840	0.717	0.878
Sensitivity	0.971	0.884	0.998
Specificity	0.533	0.328	0.596
Positive Predictive Value (PPV)	0.829	0.754	0.852
Negative Predictive Value (NPV)	0.889	0.547	0.994

Table XII showed the validity test of Urinary β2 microglobulin in the diagnosis of early DN. Urinary β2 microglobulin showed very good agreement in the diagnosis of early diabetic nephropathy according to Kappa statistics. Urinary β2 microglobulin in the diagnosis of early nephropathy in diabetic patients showed accuracy, sensitivity, specificity, PPV and NPV were 0.840, 0.971, 0.533, 0.829, and 0.889 respectively.

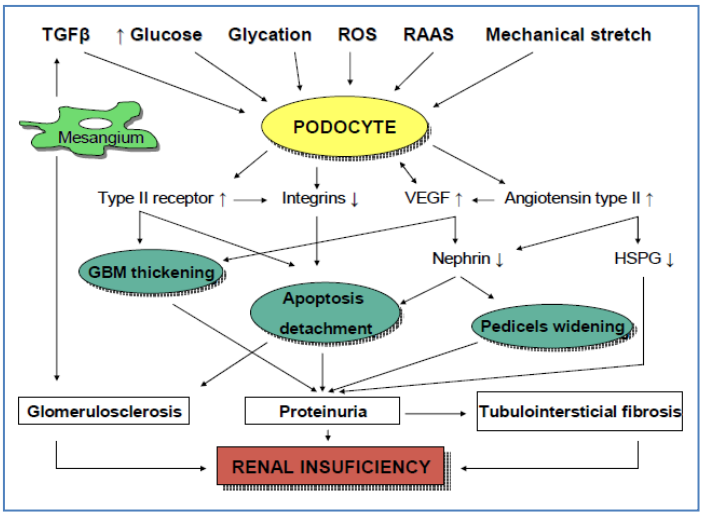

Fig-3: Mechanism of podocytes injury and development of proteinuria in diabetic nephropathy (Wolf, 2005)

DISCUSSION

In this study, most of the diabetic nephropathy patients were more than 40 years old. The mean age of the cases was 50.08 ±12.06 years and the control was 46.54±9.89 years. There was no significant difference in age between the case and control. The mean age of the diabetic nephropathy patients had a little higher than our study in the study of Ekrikpo *et al*. [20]. Age increases the risk for albuminuria [21]. Females were predominant in both case and control. Male-female ratio of diabetic nephropathy patients was 1:2.12. Females were predominant and the male-female ratio was almost similar to this study in the study of Ekrikpo *et al.* (2017) [20]. Regarding clinical history, burning sensation in limbs was observed in 11(22.0%) cases, decreased visual acuity was found in 12(24.0%) cases, numbness of hand and feet was found in 11(22.0%) cases, hypertension was found in 24(48.0%) cases. Family history of DM and HTN was found in 44(88.0%) cases and 12(24.0%) cases respectively. All patients used to take the anti-diabetic drug and 24 (48.0%) patients have taken the anti-hypertensive drug. Family history of DM and HTN was 42.2% and 10.7% [20]. The commonest long-term microvascular complication was found to be retinopathy (71.2%), followed by neuropathy (69 %). In accordance with clinical signs, the mean duration of DM, BMI, pulse, systolic BP, and diastolic BP were 6.92±4.89 years, 25.34±3.17 kg/m^2, 84.80±6.48 per minute, 120.10±15.53 mm of Hg and 73.60±9.80 mm of Hg respectively. Anemia, diabetic nephropathy, diabetic peripheral neuropathy, and autonomic neuropathy were found in 17(34.0%) cases, 14(28.0%) cases, 11(22.0%) cases, and 1(2.0%) case respectively. Mean BMI was almost similar and systolic BP and diastolic BP was a little higher in the study of Ekrikpo *et al*. [20]. The likeliness of diabetic nephropathy is higher in siblings and children of parents with diabetic nephropathy [22]. Mean RBS, HbA1c, serum creatinine, urinary ACR, and urinary β2 microglobulin of the diabetic nephropathy were 12.44 ± 6.09 mmol/L, 8.05 ± 2.15 %, 1.26 ± 0.56 mg/dl, 183.32±164.11 mg/gm and 0.50±0.22 µgm/ml respectively. Urinary protein was traced in 6(12.0%) cases, (+) in 22(44.0%) cases and (++) in 4(8.0%) cases. Mean Random plasma glucose was 12.0 ± 3.9 mmol/L and the median value of serum creatinine was 91 mmol/L [20]. Urinary ACR was found significantly higher in the case than that of control (183.32±164.11 mg/gm vs 13.60±4.40 mg/gm). Similarly, Urinary β2 microglobulin was found significantly higher in the case than that of control (0.50 ± 0.22 µgm/ml vs 0.14 ± 0.05 µgm/ml). In the study of Ekrikpo *et al*., [20]. Urinary β2 microglobulin was significantly higher in the case than in control [0.41(0.1-0.99) vs 0.1(0.1-0.41). Raised urinary ACR was found in 35(70.0%) cases and 3(6.0%) in controls. Raised ACR was significantly higher in the case than in the control. Urinary ACR was 16.68 ± 5.53 mg/gm in stages 1 & 2, 158.46±82.71 mg/gm in stage 3, and 417.66±51.33 mg/gm in stage 4 which shows progressively increased urinary ACR among different stages of DN. Raised urinary β2 microglobulin was found in 41(82.0%) cases and 2(4.0%) in controls. Raised urinary β2 microglobulin was significantly higher in the case than in the control. Urinary β2 m was 0.32 ± 0.20 µgm/ml in stage 1 & 2, 0.55 ± 0.12 µgm/ml in stage 3 and 0.63 ± 0.26 µgm/ml in stage 4 which shows progressively increased in urinary β2 m among different stages of DN. Raised urinary was found in 35(70.0%) cases and 3(6.0%) in controls. Raised ACR was significantly higher in the case than in the control. In this study, among the cases, 7 patients in stage 1 and 2 DN who had normal urinary ACR (<30.0 mg/gm) were found elevated urinary β2-M (>0.3 µgm/ml). In stage 3 and stage 4 urinary β2-M and urinary ACR raise progressively. Ekrikpo *et al*., [20] revealed, that among pre nephropathy patients diagnosed with microalbuminuria, 25 (37.9%) already had elevated urinary β2 microglobulin and among the subjects with normal urinary β2m, only 8(16.3%) had microalbuminuria. Urinary β2-M was increased in 23.5% of normoalbuminuric patients with type 2 diabetes, suggesting that proximal tubule dysfunction may be responsible for early DN independently of preceding glomerular endothelial dysfunction and urinary β2-M may be used as a sensitive marker in the diagnosis of early DN [23]. This difference in proportions was statistically significant suggesting that increases in urinary β2m may occur earlier than microalbuminuria. This finding appears to be in support of the newer pathogenetic theories of diabetic nephropathy that suggest that diabetic tubulopathy occurs earlier than diabetic glomerulopathy [24]. Measurement of β2-microglobulin in urine is a sensitive assay to detect tubular injury [25]. Urinary β2 microglobulin showed very good agreement in the diagnosis of early diabetic nephropathy according to Kappa statistics. Urinary β2 microglobulin in the diagnosis of early nephropathy in diabetic patients showed accuracy, sensitivity, specificity, PPV and NPV were 0.840, 0.971, 0.533, 0.829, and 0.889 respectively. Ekrikpo *et al*., [20] found a sensitivity of 77.8% and a specificity of 62.1%. Increased excretion of β2-m was found in the early course while albumin excretion was still in the normal range in the urine of diabetic patients, which indicated that the increase in urinary β2-M precedes the stage of albuminuria and that early DN is related to proximal tubule dysfunction [26]. In addition, the urinary excretion of β2-m increased progressively from normoalbuminuria to macroalbuminuria, indicating its value in predicting the progression of DN at an early stage [27].

LIMITATIONS

It was a single-centered study. The sample size was not reflecting the whole country scenario.

CONCLUSION & RECOMMENDATIONS

Urinary β2-m markers of tubular injury are early, sensitive, and specific markers of DN, even preceding the development of microalbuminuria, denoting that they can be used as early and sensitive markers for early detection of DN. A further large-scale study should be carried out.

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