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Assessment of prevalence of microalbuminuria as a nephropathic marker in patients suffered from type 2 diabetes mellitus and its correlation with the glycated hemoglobin

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Abstract
Diabetic nephropathy is the leading cause of end-stage renal failure in patients with Type 2 DM, and its prevalence is increasing annually worldwide. Compared to 20 years ago, the incidence of diabetic complications without diabetic nephropathy has decreased; however, is still the main complication in diabetes. Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-hrs urine collection. Microalbuminuria was the strongest predictor of cardiovascular events in a high-risk population with underlying atherosclerosis. It was found to be stronger than other risk factors such as coronary artery disease and diabetes. Microalbuminuria does not directly cause cardiovascular events; it serves as a marker for identifying those who may be at increased risk. Microalbuminuria is caused by glomerular capillary injury and so may be a marker for diffuse endothelial dysfunction. Hence based on above findings the present study was planned for Assessment of Prevalence of Microalbuminuria as a Nephropathic Marker in Patients Suffered from Type 2 Diabetes Mellitus and its Correlation with the Glycated Hemoglobin.
The present study was planned in Department of Biochemistry, Patna Medical College, Patna, Bihar, India. Total 40 cases were enrolled in the present study. The 20 cases were enrolled in Group A as cases of diabetes mellitus and 20 cases were enrolled in Group B as control cases for comparative study.
The data generated from the present study concluded that estimating glycosylated hemoglobin as an indicator of glycaemic control and microalbuminuria in random urine sample for renal involvement in diabetic subjects provide a convenient method for early diagnosis and intervention. Hence the microalbuminuria is nephrotic market in cases diagnosed with the diabetes mellitus. Hyperglycemia is the major factor initiating the changes in the kidney. The tissue damage caused by hyperglycemia can be attributed to the hemodynamic factor, glycosylation of tissue proteins and increase activity of the polyol pathway.

Keywords: microalbuminuria, nephropathic marker, type 2 diabetes mellitus, glycated hemoglobin, etc

Introduction
Microalbuminuria is a term to describe a moderate increase in the level of urine albumin. It occurs when the kidney leaks small amounts of albumin into the urine, in other words, when an abnormally high permeability for albumin in the glomerulus of the kidney occurs. Normally, the kidneys filter albumin, so if albumin is found in the urine, then it is a marker of kidney disease. The term microalbuminuria is now discouraged by Kidney Disease Improving Global Outcomes [1] and has been replaced by moderately increased albuminuria.
The level of albumin protein produced by microalbuminuria can be detected by special albumin-specific urine dipsticks, which have a lower detection threshold than standard urine dipsticks. A microalbumin urine test determines the presence of the albumin in urine. In a properly functioning body, albumin is not normally present in urine because it is retained in the bloodstream by the kidneys.
Microalbuminuria can be diagnosed from a 24-hour urine collection (between 30–300 mg/24 hours) or, more commonly, from elevated concentration in a spot sample (20 to 200 mg/l). Both must be measured on at least two of three measurements over a two- to three-month period. An albumin level above the upper limit values is called "macroalbuminuria", or sometimes just albuminuria. Sometimes, the upper limit value is given as one less (such as 300 being given as 299) to mark that the higher value (here 300) is defined as macroalbuminuria [2].
To compensate for variations in urine concentration in spot-check samples, comparing the amount of albumin in the sample against its concentration of creatinine is helpful. This is termed the albumin/creatinine ratio (ACR) and microalbuminuria is defined as ACR ≥3.5 mg/mmol (female) or ≥2.5 mg/mmol (male), or with both substances measured by mass, as an ACR between 30 and 300 µg albumin/mg creatinine. For the diagnosis of microalbuminuria, care must be taken when collecting sample for the urine ACR. An early-morning sample is preferred. The patient should refrain from heavy exercises 24 hours before the test. A repeat test should be done 3 to 6 months after the first positive test for microalbuminuria. Lastly, the test is inaccurate in a person with too much or too little muscle mass. This is due to the variation in creatinine level which is produced by the muscle [3].
Microalbuminuria is defined as excretion of 30–300 mg of albumin per 24 hours (or 20–200 mcg/min or 30–300 mcg/mg creatinine) on 2 of 3 urine collections. The detection of low levels of albumin excretion (microalbuminuria) has been linked to the identification of incipient diabetic kidney disease. This phase calls for

aggressive management, to prevent or retard overt diabetic nephropathy.

Microalbuminuria is a predictor of outcome in patients with renal disease. Additionally, it is a predictor of morbidity and mortality in patients who do not have evidence of significant renal disease. In patients with hypertension, microalbuminuria has been correlated to left ventricular hypertrophy. Both in hypertensive and normotensive patients, microalbuminuria predicts an increased risk of cardiovascular morbidity and mortality. Although 24-hour excretion has traditionally been preferred, the albumin/creatinine ratio has been shown to be a similarly valid screening tool for diabetic nephropathy [4].

Doing a 24-hour urine collection for proteinuria and creatinine clearance is unnecessary because a spot urine sample to measure urine albumin to creatinine ratio is quite sufficient for diagnosis and therapy. More importantly, exercise, dietary protein, and sustained upright posture tend to increase albumin excretion rates.

Conventional 24-hour urine collection for albumin shows wide variation in excretion of albumin in urine. Additionally, it is very inconvenient to the patient. The albumin-creatinine ratio in early morning spot urine collected on awakening (before breakfast or exercise) is considered as a valid test for albumin excretion in urine. It is simple and inexpensive; it does not require a timed 24-hour collection of urine; and, most importantly, it gives a quantitative result that correlates well with 24-hour urine values over a wide range of protein excretion. A ratio of albumin (mcg/L) to creatinine (mg/L) of less than 30 is normal; a ratio of 30-300 signifies microalbuminuria and values above 300 are considered as macroalbuminuria. On a standard urine dipstick, 10-20 mg/dL is the minimal detection limit of protein. If the dipstick is positive, then the patient likely has microalbuminuria [5]. Microalbuminuria is not detectable by the urine dipstick.

Reduction in glomerular filtration rate is usually preceded by microalbuminuria. Microalbuminuria signals the renal and cardiovascular complications from diabetes and, therefore, all diabetic patients should have their urine tested for microalbumin on an annual basis. It is unnecessary to test microalbuminuria in patients with established proteinuria. Antihypertensive therapy decreases albuminuria and diminishes its progression even in normotensive diabetic patients.

Therapy with angiotensin-converting enzyme inhibitors (ACEI) reduces the risk of overt nephropathy associated with microalbuminuria in type 1 and 2 diabetes, and similar effect is also seen in patients with type 2 diabetes treated with angiotensin receptor blockers (ARB). Insufficient data exist to validate the use of combination ACEI and ARB therapy in patients with microalbuminuria. The Heart Outcome Prevention Evaluation (HOPE) study demonstrated that diabetic patients with microalbuminuria treated with ACEI have a significantly lower risk of cardiovascular morbidity and mortality [6].

Albuminuria is a risk factor for progressive renal function loss. Albuminuria can be reduced effectively by inhibitors of renin-angiotensin system (RAS). Maximum reduction of albuminuria to the lowest possible level should be the goal of renoprotective therapy. Up-titration of benazepril or losartan against proteinuria showed further benefit on renal outcome in patients without diabetes but with proteinuria and renal insufficiency.

Diabetic nephropathy (DN), also known as diabetic kidney disease, is the chronic loss of kidney function occurring in those with diabetes mellitus. Protein loss in the urine due to damage to the glomeruli may become massive, and cause a low serum albumin with resulting generalized body swelling (edema) and result in the nephrotic syndrome. Likewise, the estimated glomerular filtration rate (eGFR) may progressively fall from a normal of over 90 ml/min/1.73m2 to less than 15, at which point the patient is said to have end-stage kidney disease (ESKD). It usually is slowly progressive over years [7].

Pathophysiologic abnormalities in DN begin with long-standing poorly controlled blood glucose levels. This is followed by multiple changes in the filtration units of the kidneys, the nephrons. (There are normally about 750,000–1.5 million nephrons in each adult kidney). Initially, there is constriction of the efferent arterioles and dilation of afferent arterioles, with resulting glomerular capillary hypertension and hyperfiltration; this gradually changes to hypofiltration over time. Concurrently, there are changes within the glomerulus itself: these include a thickening of the basement membrane, a widening of the slit membranes of the podocytes, an increase in the number of mesangial cells, and an increase in mesangial matrix. This matrix invades the glomerular capillaries and produces deposits called Kimmelstiel-Wilson nodules. The mesangial cells and matrix can progressively expand and consume the entire glomerulus, shutting off filtration [8].

The status of DN may be monitored by measuring two values: the amount of protein in the urine - proteinuria; and a blood test called the serum creatinine. The amount of the proteinuria reflects the degree of damage to any still-functioning glomeruli. The value of the serum creatinine can be used to calculate the estimated glomerular filtration rate (eGFR), which reflects the percentage of glomeruli which are no longer filtering the blood. [Citation needed] Treatment with an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), which dilates the arteriole exiting the glomerulus, thus reducing the blood pressure within the glomerular capillaries, which may slow (but not stop) progression of the disease. Three classes of diabetes medications – GLP-1 agonists, DPP-4 inhibitors, and SGLT2 inhibitors – are also thought to slow the progression of diabetic nephropathy [9].

Diabetic nephropathy is the most common cause of ESKD and is a serious complication that affects approximately one quarter of adults with diabetes in the United States. Affected individuals with end-stage kidney disease often require hemodialysis and eventually kidney transplantation to replace the failed kidney function. Diabetic nephropathy is associated with an increased risk of death in general, particularly from cardiovascular disease.

The pathophysiology of the glomerulus in DN can best be understood by considering the three involved cells as a unit: the endothelial cell, the podocyte, and the mesangial cell. These cells are in physical contact with one another at various locations within the glomerulus; they also communicate with one another chemically at a distance. All three cells are abnormal in DN [8].

Diabetes causes a number of changes to the body's metabolism and blood circulation, which likely combine to produce excess reactive oxygen species (chemically reactive molecules containing oxygen). These changes damage the kidney's glomeruli (networks of tiny blood vessels), which

leads to the hallmark feature of albumin in the urine (called albuminuria). As diabetic nephropathy progresses, a structure in the glomeruli known as the glomerular filtration barrier (GFB) is increasingly damaged. This barrier is composed of three layers including the fenestrated endothelium, the glomerular basement membrane, and the epithelial podocytes. The GFB is responsible for the highly selective filtration of blood entering the kidney's glomeruli and normally only allows the passage of water, small molecules, and very small proteins (albumin does not pass through the intact GFB). Damage to the glomerular basement membrane allows proteins in the blood to leak through, leading to proteinuria. Deposition of abnormally large amounts of mesangial matrix causes periodic-acid schiff positive nodules called Kimmelstiel–Wilson nodules [10].

High blood sugar, which leads to formation of advanced glycation end products; and cytokines have also been implicated as mechanisms for the development of diabetic nephropathy.

Diabetic nephropathy is the leading cause of end-stage renal failure in patients with Type 2 DM, and its prevalence is increasing annually worldwide. Compared to 20 years ago, the incidence of diabetic complications without diabetic nephropathy has decreased; however, is still the main complication in diabetes. Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-hrs urine collection. Microalbuminuria was the strongest predictor of cardiovascular events in a high-risk population with underlying atherosclerosis. It was found to be stronger than other risk factors such as coronary artery disease and diabetes. Microalbuminuria does not directly cause cardiovascular events; it serves as a marker for identifying those who may be at increased risk. Microalbuminuria is caused by glomerular capillary injury and so may be a marker for diffuse endothelial dysfunction. Hence based on above findings the present study was planned for Assessment of Prevalence of Microalbuminuria as a Nephropathic Marker in Patients Suffered from Type 2 Diabetes Mellitus and its Correlation with the Glycated Hemoglobin.

Methodology

The present study was planned in Department of Biochemistry, Patna Medical College, Patna, Bihar, India. Total 40 cases were enrolled in the present study. The 20 cases were enrolled in Group A as cases of diabetes mellitus and 20 cases were enrolled in Group B as control cases for comparative study.

Under aseptic precautions 4 ml of fasting venous blood samples was taken from the study subjects, allowed to stand for 30 minutes and centrifuged for 10 minutes. The serum sample was used for the estimation of FBS, PPBS (GOD/PAP method), Creatinine (Jaffe's method), Urea (Enzymatic Kinetic method), Sodium and Potassium (ISE method), whole blood sample was used for the estimation of HbA1c (Latex agglutination inhibition method). Early morning mid-stream urine sample (10 ml) in a sterile container without preservative was used for the estimation of urine microalbumin (Immuno turbidimetric method). The study parameters were estimated by using RANDOX – HA3830 autoanalyzer.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: Cases of diabetes mellitus.

Exclusion Criteria: Patients with congestive cardiac failure, urinary tract infections, nephritic syndrome, chronic glomerulonephritis, ketoacidosis, pregnancy, alcoholics were excluded from the study.

Results & Discussion

Diabetes mellitus is one of the most common metabolic diseases which is either due to the lack of hormone insulin or increase in the insulin resistance. Microvascular complications of diabetes mellitus, especially retinopathy and nephropathy are the leading causes of blindness and end stage renal disease respectively in population of both developed and developing countries. Diabetes mellitus is being increasingly recognized as a disease, which is characterized by dysfunction of the endothelium. Microalbuminuria marks the onset of endothelial dysfunction related to the kidney.

The development of diabetic nephropathy is determined by various risk factors and the level of glycemic control has been found to be the most dominant factor in the occurrence of microalbuminuria.6 Apart from such risk factors as hypertension, obesity and hypercholesterolemia, there are some genetic factors also which determine the incidence of nephropathy in these patients. More recently, genome-wide association studies identified several loci associated with an increased risk for diabetic nephropathy in both type 1 diabetes mellitus (T1DM) and T2DM [11]. Diabetic nephropathy affects approximately 25% of patients with T2DM, and represents the leading cause of end-stage renal disease in high-income countries [12]. Diabetic nephropathy is a severe complication and is related to an increased risk of all-cause mortality, cardiovascular disease, and development of end-stage renal disease, requiring expensive renal replacement therapy in the form of dialysis or transplantation [13].

Hyperglycaemia, increased blood pressure levels and genetic predisposition are the main risk factors for the development of diabetic nephropathy. Elevated serum lipids, smoking habits and the amount and origin of dietary protein also seem to play a role as risk factors.

Screening for Microalbuminuria should be performed yearly, starting 5years after diagnosis in type 1 diabetes or earlier in the presence of puberty or poor metabolic control. In patients with type 2 diabetes, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macro albuminuria should undergo an evaluation regarding the presence of co morbid associations, especially retinopathy and macro vascular disease.

Achieving the best metabolic control (HbA1c <7%), treating hypertension (<130/80 mmHg or <125/75 mmHg if proteinuria >1.0 g/24 h and increased serum creatinine), using drugs with blockade effect on the rennin angiotensin aldosterone system and treating dyslipidaemia (LDL cholesterol <100 mg/dl) are effective strategies for preventing the development of microalbuminuria, in delaying the progression to more advanced stages of nephropathy and in reducing cardiovascular mortality in patients with type 1 and type 2 diabetes [14].

Table 1: Demographic Detail

Group	Group A	Group B
Cases of	**Diabetes Cases**	**Control Cases**
No. of Cases	**20**	**20**
Age:		
31 – 40 years	3	2
41 – 50 years	5	6
51 – 60 years	8	5
61 & above years	4	7
Sex		
Males	11	7
Females	9	13

Table 2: Biochemical Parameters

Group	Group A	Group B
Cases of	**Diabetes Cases**	**Control Cases**
No. of Cases	**20**	**20**
Fasting Blood Sugar mg/ml	174.8 ± 24.9	86.9 ± 14.6
Post Prandial Blood Sugar mg/ml	249.6 ± 34.8	126.7 ± 7.8
HbA1c %	7.8 ± 1.2	5.3± 1.3
Blood Urea mg/dL	31.4 ± 5.9	14.6± 2.9
Serum Creatinine mg/dL	1.03 ± 0.2	0.91 ± 0.3
Serum Sodium mEq/L	125.4 ± 5.3	139.6 ± 3.3
Serum Potassium mEq/L	2.83 ± 0.42	3.9 ± 0.34
Microalbuminuria mg/L	43.2 ± 6.8	11.8 ± 3.9

Table 3: HbA1c & Microalbuminuria Levels

Group	Group A	Group B
Cases of	**Diabetes Cases**	**Control Cases**
No. of Cases	**20**	**20**
HbA1c %		
Less than 6.5%	4	15
More than 6.5%	16	5
Microalbuminuria		
More than 20 mg/L	14	0
Less than 20 mg/L	6	20

There is a positive link between high blood pressure (BP) and microalbuminuria. High BP may cause microalbuminuria by increasing glomerular filtration pressure and subsequent renal damage [15]. A study from Iran documented the linear relationship of the degree of microalbuminuria with BP, and duration of diabetes [16].

Fasting plasma glucose concentrations were significantly higher in the microalbuminurics compared with the normoalbuminuric. Similar results were obtained in a similar study conducted by, A. Varghese *et al*. [18].

Serum creatinine (p-0.01, S) values were found to be significantly higher in the microalbuminurics group. Similar results were obtained in a similar study conducted by, A. Varghese *et al*, [18] Muhammad Baig *et al*, [17] Benjamin A. Eghan *et al*. [19]

Nephropathy is one of the complications of type 2 diabetes mellitus that could lead to end disease. Persistent microalbuminuria is the best predictor of high risk of developing diabetic nephropathy. The relation between HbA1c and microalbuminuria with the duration of diabetes is not clear. Diabetes mellitus is the leading cause of end-stage renal disease (ESRD) in several countries.12 It is also the cause of chronic hemodialysis and renal transplantation. Several studies have suggested that detection of early changes in renal function via microalbuminuria tests prev progression of the disease.13-16 Microalbuminuria is common (prevalence rates of 10-48%) and is a well-established risk factor for macrovascular diseases in type 2 diabetics. Microalbuminuria defined as urinary albumin excretion rate of 20-200 protein excretion rate of 30-300 µg/min predicts future development of overt nephropathy [20].

Diabetic nephropathy, a common sequelae of uncontrolled diabetes, greatly affects the quality of life and contributes to decreased life expectancy. Good glycaemic control is the key to preventing the onset of diabetic nephropathy. Duration of diabetes and level glycaemic control has a significant contribution for the development of microalbuminuria by prolonged exposure to hyperglycaemia induced advanced glycosylation end products accumulation.

The findings of this study provide support for comprehensive screening for diabetes related complications especially microalbuminuria at the time of diagnosis of type 2 diabetes mellitus. Abnormal albumin excretion and other microvascular complications occur with considerable frequency before diabetes is diagnosed clinically. The relation between the development of microalbuminuria and degree of hyperglycemia indicates that early intervention towards attaining glycemic control might serve to help prevent the development of diabetic nephropathy.

Conclusion

The data generated from the present study concluded that estimating glycosylated hemoglobin as an indicator of glycaemic control and microalbuminuria in random urine sample for renal involvement in diabetic subjects provide a convenient method for early diagnosis and intervention. Hence the microalbuminuria is nephrotic market in cases diagnosed with the diabetes mellitus. Hyperglycemia is the major factor initiating the changes in the kidney. The tissue damage caused by hyperglycemia can be attributed to the hemodynamic factor, glycosylation of tissue proteins and increase activity of the polyol pathway.

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