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Evaluation of Serum Creatinine and Cockcroft-Gault Estimated GFR as an Early Biomarker of Renal Impairment in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Control of blood sugar level in Type 2 Diabetes Mellitus (DM) cases is of utmost importance in prevention of long term complications like chronic kidney disease (CKD). With an alarming increase of the incidence of Type 2 DM cases the early detection of renal impairment becomes more important. The study therefore was carried out to evaluate whether conventional biomarker like creatinine and creatinine based GFR has any implication or not for diagnosing early renal impairment in such cases.

Materials and Methods: 60 Type 2 Diabetes Mellitus patients and 60, age and sex matched healthy controls were included in the study. Routine biochemical markers like FBS, PPBS, Serum urea creatinine, Lipid profile and special parameters like HbA1c and Urine microalbumin level was measured in all of them.

Results: We have found out that serum urea and creatinine were not significantly raised in normoalbuminuric and microalbuminuric cases as compared to controls. But creatinine based GFR was significantly reduced in microalbuminuric cases when compared to controls but not significantly reduced (p=0.09) in normoalbuminuric diabetics when compared with controls.

Conclusion: Creatinine based GFR can help us to diagnose early renal impairment in Type 2 Diabetes Mellitus cases.

Keywords: Chronic kidney disease; Microalbuminuria; Diabetic nephropathy

Introduction

Diabetes Mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia [1]. The two broad categories of Diabetes are designated as Type1 and Type2 [1]. All forms of diabetes, both inherited and acquired, are characterized by a relative or absolute lack of insulin, and the development of diabetes-specific micro-vascular pathology in the retina, renal glomerulus, and peripheral nerve as well as macrovascular changes in various organ systems.

Diabetic Nephropathy is the leading cause of End Stage Renal Disease and affects approximately 40% of Type 2 Diabetic patients and most of the patients entering dialysis are diabetic [2]. Diabetic nephropathy is clinically characterized by increasing rates of urinary albumin excretion starting from normoalbuminuria, which progress to microalbuminuria then macroalbuminuria and eventually to end stage renal disease [3]. Screening for diabetic nephropathy is currently done by monitoring patients for the development of microalbuminuria and as adjunct for the estimation of GFR, the determination of serum creatinine (sCr), and creatinine clearance (CCr). The appearance of pathological levels of urinary albumin excretion (UAE) represents the most common clinical sign of early renal involvement in patients affected by diabetes mellitus [4]. Moreover, impaired renal function may be present even in patients with normal urinary albumin excretion(UAE) which further is affected by several extra renal factors [5,6].In addition, reduced kidney function is associated with increased incidence of cardiovascular morbidity and mortality [7,8].

Owing to the increased relevance of early detection and intervention in diabetic nephropathy this study was done to evaluate the serum levels of creatinine in normoalbuminuric and microalbuminuric patients with type 2 diabetes mellitus.

Materials and Methods

The study was conducted in the Department of Biochemistry, S.C.B. Medical College and Hospital, Cuttack from February 2014 to April 2015.

60 patients of type 2 diabetes of age group 35-60 years, attending OPD and indoor in the Department of Medicine, S.C.B. Medical College and Hospital, Cuttack, were included in the study. Patients with Type 2 Diabetes Mellitus were selected and diagnosed on the basis of their history, physical examination, biochemical investigations and according to the Criteria for the diagnosis of Diabetes Mellitus given by WHO 2011 [1].

The control group consisted of 60 age and sex matched healthy adults with normal plasma glucose levels, no symptoms

suggestive of diabetes mellitus and no family history of the disease, no history of any kind of kidney disease.

3 ml of blood was collected after overnight fasting of 8 hours from all enrolled patients and healthy controls for the assessment of serum creatinine and other biochemical parameters. Finger prick blood sample was taken at the same time for assessment of HbA1C levels from all patients and healthy controls.

For evaluation of urine microalbumin by immunoturbidometric assay early morning midstream urine samples were collected.

Biochemical parameters done are:

- Fasting plasma glucose and post prandial plasma glucose (GOD-POD method)
- Serum urea (GLDH/ Kinetic method), serum creatinine (Modified Jaffe method)
- Serum cholesterol (CHOD-PAP method), serum triglycerides (enzymatic method), serum HDL (turbidometric immunoassay method), serum LDL (Friedwald's formula) , serum VLDL(calculated).

Special parameters:

- Urine microalbumin by immunoturbidometric assay
- Capillary blood HbA1c level

Inclusion Criteria:

Cases of diabetes mellitus were diagnosed according to the Criteria for the diagnosis of Diabetes Mellitus given by WHO 2011.

Any of the following is diagnostic:

- Classic symptoms of diabetes and random plasma glucose concentration ≥ 200 mg/dl
- Fasting plasma glucose ≥ 126 mg/dl
- A1C>6.5%
- 2-hour post load plasma glucose concentration ≥ 200 mg/dl during the OGTT
- The control group consisted of age and sex matched healthy adults with fasting plasma glucose levels ≤ 99 mg/dl and post prandial plasma glucose ≤ 139 mg/dl.

Exclusion Criteria:

Patients with

- Chronic kidney disease due to any cause
- Thyroid disorders,
- Patients under thyroid medications.
- Patients under steroid therapy
- Uncontrolled hypertensive patients
- Cardiovascular disease patients

Observation

Table 1: Characteristics of control group and study group. *statistically non-significant as compared to controls. **Statistically significant ($p<0.01$) as compared to control and normoalbuminurics.

Sl No.	Parameter	Control group (n=60)	Study Group (n=60)	
			normoalbuminuic	microalbuminuric
		Mean ± SD	Mean ± SD	Mean ± SD
1	Age (in years)	47.64 ± 7.94	50.42 ± 4.57	55.59 ± 5.57**
2	BMI (Kg/m^2)	24.27 ± 2.28	24.47 ± 1.84*	25.09 ± 1.73**
3	Duration of diabetes (in years)	-	7.10 ± 2.55	10.52 ± 4.60

Table 2: Comparision of FPG, PPPG and HbA1C % of the control and study group. *Statistically significant ($p<0.01$) compared to controls. **Statistically significant ($p<0.01$) compared to controls and normoalbuminuric cases.

Sl No.	Parameter	Control group (n=60)	Study Group (n=60)	
			Normo-albuminuric	Micro-albuminuric
		Mean ± SD	Mean ± SD	Mean ± SD
1	FPG(mg/dl)	83.72 ± 8.25	145.65 ± 23.34*	183.88 ± 24.69**
2	PPPG(mg/dl)	102.77 ± 11.18	208.97 ± 33.41*	233.85 ± 39.27**
3	HbA1C(%)	4.67 ± 0.39	7.3 ± 1.5*	7.9 ± 1.3**

Table 3: Serum urea and creatinine in control group and study group. There was no significant increase in either urea or creatinine in cases when compared to controls.

Sl No.	Parameter	Control Group (n =60)	Study Group (n=60)	
			Normo-albuminuric	Micro-albuminuric
		Mean ± SD	Mean ± SD	Mean ± SD
1	Serum Urea	22.84 ± 6.04	29.71 ± 3.41	33.23 ± 15.17

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	(mg/dl)			
2	SerumCreatinine (mg/dl)	0.90 ± 0.26	0.97 ± 0.17	1.10 ± 0.21

Table 4: Lipid Profile of Control Group and Study Group. *Statistically significant (p<0.05) as compared to control group. #Statistically non-significant(p=0.16) as compared to normoalbuminuric. ΩStatistically significant as compared to normoalbuminuric (p<0.05).

Sl No.	Parameter (mg/dl)	Control Group (n=60)	Study Group (n=60)	
			Normo-albuminuric(n=28)	Micro-albuminuric(n=32)
		Mean ± SD	Mean ± SD	Mean ± SD
1	Total Cholesterol (TC)	163.82 ± 18.50	193.61 ± 20.98*	195.81 ± 37.33*#
2	Triglycerides (TG)	136.78 ± 31.89	178.90 ± 20.33*	217.13 ± 33.13 Ω
3	HDLc	46.54 ± 4.32	43.35 ± 4.58	39.61 ± 2.70 Ω
4	LDLc	89.62 ± 17.73	116.82 ± 19.33*	135.35 ± 33.75 Ω
5	VLDLc	24.26 ± 4.19	27.91 ± 3.98*	34.49 ± 6.64 Ω

Table-5: Spot urinary albumin excretion(in mg/l)in the study group. Shows the mean spot urine albumin excretion(UAE) in mg/L in the normoalbuminuric DM patients to be 21.4 ± 6.21 and in the microalbuminuric DM cases the mean spot urine albumin excretion was found to be 113 ± 63.80.

Category		UAE(mean ± SD)	P value
Study group (n=60)	Normoalbuminuric cases (n=28)	21.4 ± 6.21	<0.0001
	Microalbuminuric cases (n=32)	113 ± 63.80	

The mean UAE was found to be higher in the microalbuminuric cases than the normoalbuminuric cases which was statistically significant (p<0.0001)

Table 6: Comparision of c-g based e-GFR between study and control group. Shows that the mean e-GFR calculated by C-G formula in the control group was 124.36±12.55(ml/min/1.73m^2). Similarly in the normoalbuminuric DM cases mean C-Ge-GFR is 103.37±19.10(ml/min/1.73m^2) and in the microalbuminuric DM cases the mean C-Ge-GFR is 75.73±11.39 (ml/min/1.73m^2).

Parameter	Control group (n=60) Mean ± SD	Study group (n=60)	
		Normo-albuminuric cases (n=28)	Micro-albuminuric cases (n=32)
Cockcroaft-Gault (e-GFR) (ml/min/1.73m²)	124.36 ± 12.55	103.37 ± 19.10*	75.73 ± 11.39**

Table 7: Correlation of serum creatinine concentration with urinary albumin excretion (uae) in type 2 dm patients. Shows the correlation study between serum creatinine concentration with UAE in patients of type 2 diabetes mellitus. A significant positive correlation was observed with a r value of 0.478 and p value of <0.05 for creatinine.

	R value	P value
Serum Creatinine *vs.* UAE	0.478	<0.05

Results and Discussion

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood (hyperglycemia).It is the most common endocrine disease ,characterized by metabolic abnormalities and long term complications involving the eyes , kidneys ,nerves and blood vessels. Several distinct types of DM exist and are caused by a complex interaction of genetics and environmental factors. The two broad categories of DM are designated type 1 and type 2. Type 1 diabetes is the result of complete or near-total insulin deficiency. Type 2 DM is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production [1].

Diabetic nephropathy is one of the important long term complications of diabetes and the leading cause of death and disability in diabetes. Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. It is the leading cause of end stage renal disease (ESRD) in the United States and a leading cause of DM related mortality and morbidity. Both microalbuminuria and macroalbuminuria in individuals with DM are associated with increased risk of cardiovascular disease. Individuals with diabetic nephropathy commonly have diabetic retinopathy.

In diabetic nephropathy glomerular hyperperfusion and renal hypertrophy occurs at the early stages of DM and are associated with an increase in GFR During first 5 yrs of DM, thickening of the glomerular basement membrane, glomerular hypertrophy occurs as the GFR returns to normal. After 5-10 years 40% individuals begin to excrete small volumes of albumin in urine. Although the appearance of microalbuminuria(30-299 mg/day albumin in urine) is an important risk factor for progression to macroalbuminuria(>300 mg/day albumin in urine) ,only 50% individuals progress to macroalbuminuria over the next 10 years. Once macroalbuminuria is present, there is a steady decline in GFR and 50% individuals reach ESRD in 7-10 years.

The GFR is generally considered to be the best index of renal function in health and disease. Rigorous assessment of GFR requires the measurement of an ideal filtration marker, defined as a substance that is freely filtered by the kidney, not bound to plasma proteins, non-toxic and does not undergo metabolism, tubular secretion or absorption. The clearance of endogenous creatinine is commonly used, despite its limitations.

The present study was thus undertaken to evaluate the serum levels of creatinine in normo and microalbuminuric type 2 diabetics. The present study has tried to explore the usefulness of creatinine and C-G GFR as a marker of early renal involvement in diabetic patients which in turn can help in their timely intervention.

In this study a total of 120 subjects were selected out of which 60 persons were type 2 diabetes mellitus cases and 60 individuals served as age and sex matched controls.

The mean age in the microalbuminuric DM cases was significantly higher ($p<0.01$) than the controls as well normoalbuminuric DM cases (Table 1).

In normoalbuminuric DM cases mean BMI was 24.47 ± 1.84 and in microalbuminurics mean BMI was 25.09 ± 1.73 which was significantly raised as compared to normoalbuminuric group and controls. This confirms the fact that higher BMI is a risk factor for diabetes [1]. However the BMI of normoalbuminuric cases when compared to healthy controls did not show any significant difference. ($p=0.13$)(Table 1).

The mean FPG was found to be significantly raised ($p \leq 0.01$) in both normoalbuminuric cases and microalbuminuric cases when compared to healthy controls. The mean PPPG was found to be significantly raised ($p \leq 0.01$) in both normoalbuminuric cases and microalbuminuric cases when compared to healthy controls (Table 2). Metabolic abnormalities such as insulin resistance, impaired insulin secretion and increased hepatic glucose production are the reasons for this rise in FPG and PPPG1.

The mean HbA1C (%) in control was significantly raised ($p<0.01$) in normoalbuminuric and microalbuminuric cases.Poor glycemic control is well defined contributor to the development and progression of microalbuminuria among Type 2 patients [9]. Monnier, et al. 2003 [10] demonstrated importance of PPBS to increase in HbAIC% level.Higher PPBS will produce increased AGE (advanced glycation End products) and oxidative stress thereby producing microvascular complication like diabetic nephropathy.

Serum urea and creatinine were not significantly increased in cases as compared to controls(Table 3).Urea concentration in the blood can vary with diet, hepatic function, and numerous disease states. It is freely filtered by the glomerulus and not secreted by the tubules, but about (40–70%) is passively reabsorbed from the renal tubules [11]. Serum creatinine level does not increase significantly until the GFR is reduced to less than 50% of its normal value (Perrone, et al. 1992) because of increased tubular secretion of creatinine [12].

In the present study the serum total cholesterol (TC) was significantly raised ($p<0.05$) in the normoalbuminuric cases than in controls,where as it was not significantly raised($p=0.16$) in microalbuminuric DM cases compared to normoalbuminuric cases. Serum triglycerides (TG), and LDL and VLDLc were significantly higher ($P<0.05$) in normoalbuminuric diabetic patients compared to controls and further increased in microalbuminuric cases compared to normoalbuminurics ($p<0.05$), while HDL was significantly lower P<(0.05) in microalbuminuric diabeticsas compared to controls (Table 4).

This observation of our study coincided with the observation of Mahato RV, et al. Several cross-sectional studies have suggested that raised lipid levels are involved in the pathogenesis and progression of renal diseases [13]. This may be due to insulin resistance in adipose tissue as a result of which free fatty acid (FFA) flux from adipocytes is increased, leading to increased lipid synthesis in hepatocytes [elevated triglycerides, reduced high-density lipoprotein (HDL), and increased small dense low-density lipoprotein (LDL) particles] [1].

The mean spot urinary albumin excretion was found to be higher in the microalbuminuric cases than the normoalbuminuric cases which was statistically significant ($p<0.0001$) (Table 5). Abu Hilal [14] and Abu Mustafa [15] also documented similar finding. Normally albumin does not escape into the urinary space due the filtration barrier. Long standing diabetes leads to damage to glomerular basement membrane thus altering the filtration efficiency of kidneys and leaking of albumin into urine.

GFR is usually accepted as the best overall estimate of kidney function and therefore is commonly used to evaluate onset and progression of CKD in various groups including diabetes.C-G (Cockcroft-Gault) formula [16] based (C-G e-GFR). The mean C-G e-GFR (ml/min/1.73m²) calculated in the controls, normoalbuminuric and microalbuminuric diabetes mellitus cases were 124.36 ± 12.55; 103.37 ± 19.10; and 75.73±11.39 respectively. C-G e-GFR is significantly reduced ($p<0.05$) only in the microalbuminuric cases as compared to controls but not in normoalbuminuric cases ($p=0.09$) compared to controls (Table 6).

With advance in diabetes and consequent hyperglycemia induced damage to the podocytes and basement membrane increases the permeability to albumin [17].Co-exsistent glomerulosclerosis and basement membrane thickening causes decreased filtration function of kidney. Consequently this leads to rise in the serum levels creatinine as it is exclusively filtered by the glomerulus with catabolism in tubules without tubular secretion.

Summary

The present study entitled "*Evaluation of serum creatinine and Cockcroft-Gault estimated GFR(C-G eGFR) as an early biomarker of renal impairment in patients with type 2 diabetes mellitus.*" was carried out with an objective to observe alteration in serum creatinine levels in patients of type 2 diabetes mellitus and its correlation with the degree of urine albumin excretion.

In this study the 60 diabetic patients were divided based upon their spot urinary albumin excretion into 28 normoalbuminuric

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(UAE<30 mg/L) and 32 microalbuminuric cases (UAE 30-300 mg/L).The control group consisted 60 age and sex matched healthy adults. The biochemical investigations like plasma glucose, serum lipids, serum urea and creatinine, HbA1c % and urinary albumin estimation was done in both controls and cases. GFR was calculated according C-G formula.

Microalbuminuric diabetics had a higher mean age and BMI as compared to controls and normoalbuminuric cases.

The mean FPG, PPPG and HbA1c % was significantly increased in microalbuminuric cases compared to controls and normoalbuminuric cases.

Serum urea and creatinine were not significantly raised in normoalbuminuric and microalbuminuric cases as compared to controls.

Serum total cholesterol (TC) was significantly raised in normoalbuminurics when compared with controls, but was not significantly raised (p=0.16) in microalbuminuric cases as compared to normoalbuminurics. But serum triglycerides, LDLand VLDL were significantly raised(p<0.05) in normoalbuminurics compared to controls as well in microalbuminurics cases when compared to normoalbuminurics while HDL was significantly lower in microalbuminuric(p<0.05) compared with controls.

C-G GFR(ml/min/1.73m^2) was only significantly reduced in microalbuminuric cases when compared to controls but not significantly reduced(p=0.09) in normoalbuminuric diabetics when compared with controls.

Conclusion

It is already established that creatinine is a sensitive marker for predicting renal damage in Type 2 DM cases, but in our study C-G GFR, not creatinine was found to be significantly reduced in type 2 DM cases with microalbuminuria.

Therefore according to our study, C-G GFR, not creatinine can serve as a reliable indicator for predicting renal impairment in an early stage in Type 2 Diabetes Mellitus cases.

Limitations

Certain limitations were also there in our study. As ours is a cross sectional study, we cannot determine causality. The number of cases and controls were also limited. The results can be further established by increasing the sample size as well as by increasing the duration and by doing follow up investigations of the patients after certain period of time.

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