International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2015): 6.391

Study of eGFR in Type-2 Diabetes Mellitus

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Abstract: ***Introduction:*** ***Diabetic nephropathy (DN) is one of the most serious microvascular complication of Type-2 Diabetes Mellitus (Type-2 DM) which significantly impacts morbidity, mortality and quality of life. Estimated GFR is potentially an excellent method of detecting and monitoring renal failure.*** ***Objectives:*** ***To estimate and evaluate the correlation of fasting blood glucose, blood urea, serum creatinine & eGFR as biomarkers in detection of renal dysfunction in Type-2 diabetics as compared to healthy controls.*** ***Methodology:*** ***In this study, 50 proven cases of Type-2 Diabetic patients and an equal number of age and sex matched healthy controls were included.*** ***Results:*** ***The serum concentrations of FBG, Urea and Creatinine were increased and eGFR was decreased in Type-2 diabetic patients and were statistically highly significant (p, <0.001). There is a negative correlation between urea and creatinine with eGFR which is statistically highly significant (p, <0.001).*** ***Conclusion:*** ***Estimation of GFR would allow to detect and stage the degree of renal impairment in diabetic nephropathy. Estimation of GFR using an appropriate method is a reliable measure of the kidney function and impairment in diabetic nephropathy.***

Keywords: Type-2 DM; Diabetic Nephropathy; eGFR.

1. Introduction

Diabetes mellitus (DM) is a syndrome of chronic hyperglycemia due to relative insulin deficiency, resistance or both. It affects more than 120 million people world-wide and it is estimated that it will affect 370 million by the year 2030.[1] According to the Indian Heart Association; India is the diabetes capital of the world with a projected 109 million individuals with diabetes by 2035. The disease currently affects more than 62 million Indians, which is more than 7.1% of India's adult population.[2]

Diabetic Nephropathy (DN) is the single most common cause of chronic renal failure (CRF) and is a rapidly growing problem worldwide. It is an acquired sclerotic injury associated with thickening of the glomerular basement membrane secondary to long standing effects of hyperglycaemia, advanced glycation end products and reactive oxygen species.[3] Diabetic nephropathy develops due to a complex interaction between metabolic and haemodynamic pathophysiological factors, which lead to renal damage.[4]

GFR is a useful index to assess kidney function. GFR is best measured by injecting compounds such as inulin, radioisotopes such as ^{51}Chromium- EDTA, ^{125}I-iothalamate, ^{99m}Tc-DTPA or radio contrast agents such as iohexol. These tests are complicated, costly, time-consuming and have potential side-effects.[5] Endogenous markers like plasma creatinine and urea concentration despite their limitations are commonly used because they are cheap and easily available.[6]

Urea is freely filtered by the glomerulus and not secreted by the tubules. However, a large portion (40-70%) is passively reabsorbed from renal tubules leading to underestimation of GFR and also its concentration in plasma may vary depending on diet, hepatic function and state of numerous diseases.[6]

Serum creatinine is the most widely used parameter for everyday assessment of GFR, but it has poor sensitivity & specificity in acute renal failure (ARF) because serum creatinine lags behind both renal injury and renal recovery.[7] It is an insensitive indicator of diminished GFR because its concentration is affected by meat intake, gender, muscle mass, malnutrition and aging.[6]To circumvent these limitations, several equations have been developed to estimate GFR from serum concentration. The most popular equation used today is the Modification of Diet in Renal Disease (MDRD) equation.[8]

This study is being undertaken to determine the utility of eGFRin predicting the decline of renal function in diabetes. Thus, appropriate & timely interventions can be instituted to delay or arrest the progression of diabetic nephropathy.

Aim and Objectives

Aim: The aim of the study is to estimate early decline in GFR in diabetes.

Objectives

1. To estimate the concentrations of fasting blood glucose, blood urea, serum creatinine & eGFR in Type-2 diabetics and healthy controls.
2. To evaluate the correlation of fasting blood glucose, blood urea, serum creatinine & eGFR as biomarkers in detection of renal dysfunction in Type-2 diabetics as compared to healthy controls.

2. Methodology

A case-control study was taken up in group of Type-2 diabetic patients with age and sex matched healthy controls selected from S.S Hospital attached to SSIMS & RC, DAVANGERE during the study period from November-2013 to August-2015.

The study was approved by the ethical and research committee of SSIMS &RC, Davangere to use human

subjects in the research study. Written informed consent was taken from the study subjects.

Patients were selected from the outpatient and inpatient departments of medicine in the hospital. A total of 50 proven cases of Type-2 diabetic patients in the age group of 30-80 years were included. All patients suffering from Type-2 diabetes diagnosed and confirmed by physician with FBG (fasting blood glucose) and PPBS (post prandial blood sugar) according to American Diabetes Association criteria (FBG ≥126 mg/dL and 2 hour PPBS ≥200 mg/dL). A total of 50age and sex matched healthy peoples without any major illness and not on any medications were included.

Fasting blood glucose, Creatinine and urea were analysed by using Erba kit in Semi Auto Analyzer and eGFR was calculated by MDRD equation.

Statistical analysis

Continuous variables with normal distributionwere compared using students t-test.Categorical variables were compared using chi square test. Correlation between FBG, UREA, CREATININE and eGFR were studied using Pearson's correlation coefficient. Statistical analysis was done using Statistical Package for SocialSciences (SPSS) version 20. A p-value less than 0.05 wasconsidered statistically significant.

3. Results

The results obtained in this present study were from total number of 100 subjects.

Table 1: Shows age and sex-wise distribution of Healthy Controls and Type-2 diabetic patients

Age groups (yrs)	Healthy Controls		Type-2 DM	
	No.	(%)	No.	(%)
30 - 39	5	10%	1	2%
40 - 49	19	38%	16	32%
50 - 59	9	18%	8	16%
60 - 69	12	24%	12	24%
70 - 80	5	10%	13	26%
Total	50	100%	50	100%
Mean ± SD	52.98 ±11.16		56.5 ± 11.67	
p-Value, Sig	0.152, NS			
Males	34	68%	28	56%
Females	16	32%	22	44%
Total	50	100%	50	100%
p-Value, Sig	0.216, NS			

NS (Not Significant)

Table 1: Show age and sex-wise distribution of subjects studied. A total number of 100 subjects were studied. Among them, 50 were healthy controls who were normal healthy individuals without any disease which includes 34 male and 16 female subjects and 50 were Type-2 diabetic patients which includes 28 male and 22 female subjects. The incidence of Type-2 diabetes was higher in the age group of 40-49 years as compared to same age group in healthy controls.

Table 2: Shows the mean serum concentrations of FBG, Blood Urea, Creatinine and eGFR in Healthy Controls and Type-2 diabetic patients

Parameters	Healthy Controls	Type-2 DM	p -Value, Sig
	Mean ± SD	Mean ± SD	
FBG (mg/dl)	92.42 ± 13.36	221.48 ± 89.62	<0.001, **
UREA (mg/dl)	23.47 ± 8.53	68.84 ± 30.76	<0.001, **
Creatinine (mg/dl)	0.85 ± 0.43	3.30 ± 1.60	<0.001, **
eGFR(ml/min)	102.21 ± 20.71	23.27 ± 13.75	<0.001, **

Student's unpaired t-test, $p > 0.05$ NS (Not Significant), $p < 0.05$ *S (Significant), $p < 0.001$ **HS (Highly Significant)

Bar Diagram 1: Shows comparison of FBG, UREA, CREATININE and eGFR in Healthy Controls and Type-2 DM

Table 2 and Bar diagram 1: Show comparison of fasting blood glucose, blood urea, serum creatinine and eGFR between healthy controls and Type-2 diabetic patients.

It is seen from the table that concentrations of fasting blood glucose, blood urea, serum creatinine and eGFR in healthy controls were in the range of 92.42 ± 13.36, 23.47 ± 8.53, 0.85 ± 0.43 and 102.21 ± 20.71, respectively. In Type-2 diabetic patients they were in the range of 221.48 ± 89.62, 68.84 ± 30.76, 3.30 ± 1.60 and 23.27 ± 13.75, respectively.

Statistical analysis by student's unpaired t-test showed that the mean concentrations of fasting blood glucose, blood urea and serum creatinine were increased and eGFR was decreased in Type-2 diabetic patients when compared to healthy controls and were statistically highly significant (p, <0.001).

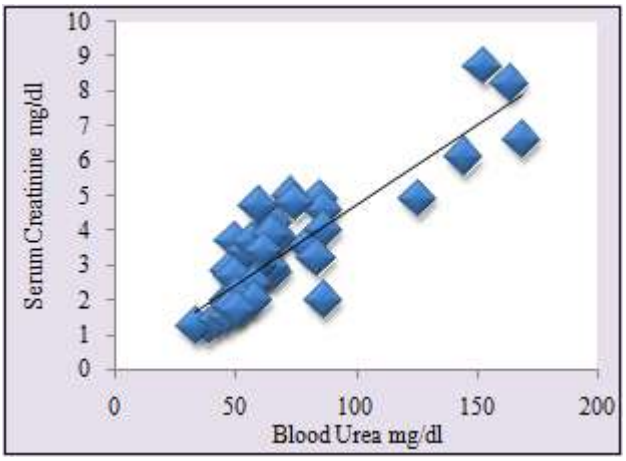
Table 3: Shows Karl Pearson's correlation coefficient (r) matrix of FBG, Urea, Creatinine and eGFR in Type-2 diabetic patients

		FBG	Urea	Creatinine	eGFR
FBG	r value	1	0.134	0.169	-0.209
	p-value		0.352	0.240	0.145
Urea	r value		1	0.874**	-0.588**
	p-value			<0.001	<0.001
Creatinine	r value			1	-0.768**
	p-value				<0.001
eGFR	r value				1
	p-value				

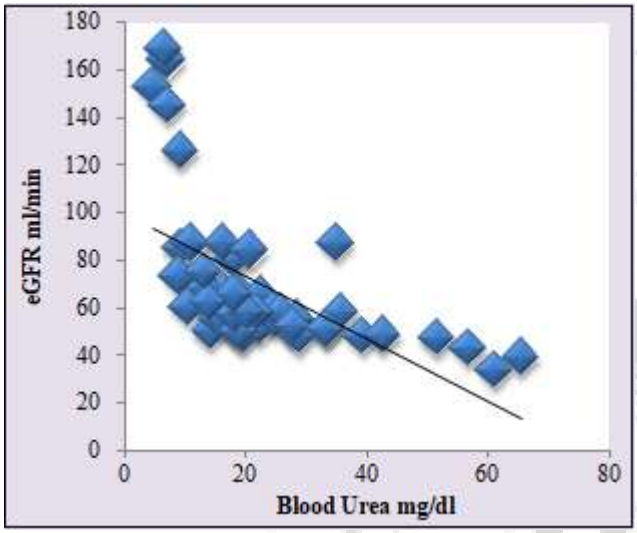
*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is highly significant at the 0.01 level (2-tailed).

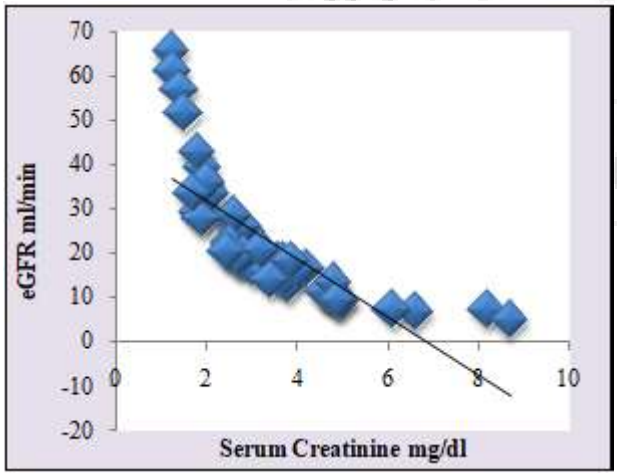
r = Karl Pearson's coefficient of correlation



Scatter plot 1: Shows correlation between Serum Creatinine and Blood Urea in Type-2 DM



Scatter plot 2: Shows correlation between eGFR and Blood Urea in Type-2 DM



Scatter plot 3: Shows correlation between eGFR and Serum Creatinine in Type-2 DM

Table 3 and Scatter plots 1 to 3: Show the Karl Pearson's correlation between FBG, Urea, Creatinine and eGFR in Type-2 diabetic patients.It is evident from the table that there is a highly statistically significant positive correlation between urea v/s creatinine, (p, <0.001). There is a positive correlation between FBG, Urea and Creatinine but is not statistically significant.

There is a negative correlation between urea and creatinine with eGFR which is statistically highly significant (p, <0.001). There is also a negative correlation between FBG and eGFR but it is not statistically significant.

4. Discussion

Diabetic nephropathy is the most common cause of chronic kidney disease which is widely prevalent in developing countries. Diabetic nephropathy develops due to complex interaction between metabolic and haemodynamic pathophysiological factors, which lead to renal damage. It presents with microalbuminuria in the earliest stage. This may progress to macroalbuminuria and later renal insufficiency and ESRD.

In the present study we have included 100 subjects, comprising of 50 Type-2 diabetic patients and 50 healthy controls. Among 50 Type-2 diabetic patients, 28 are male and 22 are female patients and among 50 healthy controls, 34 are male and 16 are females. The peak incidence of Type-2 DM was observed to be between age groups of 40-49 years and considering sex incidence, men had higher incidence (about 28) when compared to women (22 patients).

In this study, we have evaluated the serum concentrations of FBG, Urea, Creatinine and calculated eGFR in healthy controls and Type-2 DM.

Creatinine:
Creatinine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body (depending on muscle mass). Elevated levels are found in renal dysfunction, reduced blood flow (shock, dehydration and congestive heart failure), diabetes and acromegaly. Decreased levels are found in muscular dystrophy. Glomerular filtration rate is considered the best marker of renal function and serum creatinine is the most commonly used biochemical parameter to estimate GFR in routine practice. Although the best measure for GFR is obtained by techniques that involve infusion of either endogenous or exogenous substances, GFR is usually estimated in clinical practice by various formulae based on serum creatinine concentration.

The mean serum concentrations of creatinine in healthy controls and Type-2 diabetic patients were in the range of 0.85 ± 0.43 mg/dl and 3.30 ± 1.60 mg/dl, respectively. The mean concentration of serum creatinine in Type-2 diabetic patients was higher when compared to healthy controls. The eGFR in healthy controls and Type-2 diabetic patients were in the range of 102.21 ± 20.71 ml/min and 23.27 ± 13.75 ml/min, respectively. Creatinine correlated positively with urea but it negatively correlated with eGFR and which were statistically highly significant (p, <0.001).

In diabetic nephropathy, the cause of decreased GFR is due to loss of integrity of the glomerular basement membrane. Estimation of the GFR is the most widely used test of renal function and reflects the kidney's ability to clear a particular substance from plasma. The small molecule

creatinine is endogenously produced by muscles and excreted by the kidneys. Therefore, a reduction in GFR leads to an increase in serum creatinine.

Our findings of the study is in agreement with several other studies,[1,9,10]

Hany S. Elbarbary, et al., showed that serum creatinine levels were increased in microalbuminuric Type-2 DM patients when compared to normoalbuminuria. There was a significant negative correlation between serum creatinine and eGFR.[1]

A G Christensson, et al., found that serum creatinine as a GFR marker. Their study infers that age-adjusted serum creatinine seems to be as good in the diagnosis of severe nephropathy.[9]

Ashwin Kumar A S, et al., showed that serum creatinine was significantly elevated in the study group as compared to non-diabetic controls. There was a strong negative correlation of serum creatinine with GFR. Serum creatinine can be used as an marker in determining GFR in Type-2 diabetes mellitus.[10]

Strength and further scope of the study:
The concentrations of creatinine and urea were significantly increased in Type-2 diabetic patients as compared to healthy controls except eGFR which was significantly decreased in Type-2 diabetic patients as compared to healthy controls.

The diagnosis of diabetic nephropathy can be improved by measuring several new biochemical markers that have the potential to detect early renal impairment in Type-2 DM than the traditional markers. These new markers include cystatin-C, Kidney Injury Molecule-1 (KIM-1), N-acetyl-β-glucosaminidase (NAG), human neutrophil gelatinase-associated lipocalin (NGAL), β2-microglobulin, α1-microglobulin, transferrin, type-IV collagen, interleukin-18 (IL-18), clusterin and ceruloplasmin.

5. Conclusion

Diabetic nephropathy is an important microvascular complication which is one of the most common cause of morbidity and mortality of Type-2 diabetes mellitus. It is the consequence of metabolic derangement of diabetic state. A large proportion of patients with impaired renal function were not diagnosed if clinicians rely solely on normal serum creatinine as evidence of normal renal function. Estimated GFR is potentially an excellent method of detecting and monitoring renal failure, as it is quick, cheap and simple.

Estimation of GFR using an appropriate method is a reliable measure of the kidney function and impairment in diabetic nephropathy. Together with the availability of new, sensitive, non-invasive serum markers, an accurate estimation of GFR appears to be important because nearly 40% of ESRD patients receiving renal replacement therapy already have diabetes mellitus.

The inadequacy of the traditional markers in detecting early changes in GFR and particularly in monitoring the course of advanced diabetic nephropathy calls for alternative non-invasive methods in clinical nephrology. The more prominent rise in serum creatinine values, as found in this study, allows a more rapid diagnosis of decline in GFR, with an earlier therapeutic intervention.

Our results show that estimation of GFR by using creatinine value for renal glomerular function assessment in a well-defined patient group and may be recommended in the routine management of diabetic patients. So serial measurement of creatinine along with eGFRwould allow to detect and stage the degree of renal impairment in diabetic nephropathy and would indicate how the disease evolves in these patients, allowing us to adopt early measures to control the disease.

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