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RESEARCH ARTICLE

Correlation of serum creatinine and urea with glycemic index and duration of diabetes in Type 1 and Type 2 diabetes mellitus: A comparative study

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ABSTRACT

Background: Diabetes is a common cause of end-stage renal disease and nephropathy, which is characterized by abnormal renal function with reduction of glomerular filtration and rise in the level of serum urea and creatinine. **Aims and Objectives:** The aim of this study was to compare serum urea and creatinine levels in Type 1 and Type 2 diabetics and further correlate the serum creatinine and urea levels in both Type 1 and Type 2 diabetic subjects with duration of diabetes and glycosylated hemoglobin levels (HbA1c). **Materials and Methods:** Blood samples were collected and analyzed for serum urea and creatinine levels in diabetic subjects, both Type 1 and Type 2 attending diabetic clinic and non-diabetic subjects in a tertiary hospital. 72 male subjects in each group of age 35-55 years were selected for the study. Fasting, post-meal blood sugar levels, and HbA1c of all the subjects in the study were determined. Results were interpreted by one-way analysis of variance test. Association of serum urea and creatinine levels with HbA1c and duration of illness in all diabetic subjects was analyzed by applying Pearson's correlation coefficient. **Results:** There was statistically significant increase in serum urea and creatinine levels in both Type 1 and Type 2 diabetic subjects compared to non-diabetic subjects. There was a correlation of levels of serum urea and creatinine with HbA1c levels and duration of diabetes in Type 1 diabetics but not with Type 2 diabetic study group. **Conclusion:** Serum urea and creatinine are simple and useful biomarkers which can serve as predictor tests for assessing kidney functions (nephropathy) in diabetic patients.

KEY WORDS: Blood Urea; Creatinine; Type 1 Diabetes; Type 2 Diabetes; Nephropathy; Glycosylated Hemoglobin

INTRODUCTION

Diabetes mellitus is reaching potentially epidemic proportions in India. The level of morbidity and mortality due to diabetes and its potential complications are enormous.[1] The chronic hyperglycemia of diabetes is associated with damage and failure of various organs, especially the eyes, kidneys, nerves, heart, and vascular system. Diabetes is the major cause of end-stage renal disease and diabetic nephropathy which are also called as diabetic kidney disease. It has been suggested that in lifetime 25-45% of the diabetic patients would be developing clinically evident diabetic nephropathy. After the onset of the disease, the peak onset of nephropathy in Type 1 diabetes is between 10 and 15 years. The patients having no proteinuria have a risk of developing overt renal disease after 25 years of only about 1%/year.

Glycosylation of tissue proteins may contribute to diabetic nephropathy apart from other microvascular complications. In diabetes mellitus, hyperglycemia causes the excess of

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glucose to combine with free amino acids on circulating or tissue proteins. This non-enzymatic process initially forms reversible early glycosylation products and later irreversible advanced glycosylation end-products (AGEs) via an Amadori rearrangement. The tissue accumulation of AGEs, by crosslinking with collagen, can contribute to the associated renal and microvascular complications.[2] Good glycemic control can reduce the incidence of diabetic nephropathy. The earliest detectable abnormality of nephropathy is microalbuminuria followed by decrease in glomerular filtration rate (GFR) and increase in serum creatinine concentrations.[3] This study was planned with the objectives: (i) To measure and compare the levels of serum urea and serum creatinine in Type 1 and Type 2 diabetic subjects with those of non-diabetic subjects and (ii) to correlate the relationship of serum urea and creatinine levels in diabetic subjects with duration of diabetes and glycosylated hemoglobin levels (HbA1c).

MATERIALS AND METHODS

This study was conducted in a tertiary hospital after obtaining approval from the Institutional Ethical Review Committee. All the subjects were males of the age 30-55 years of age. The study comprised Type 1 and Type 2 diabetic patients, 72 in each group, attending the diabetic clinic and 72 non-diabetic subjects who were selected from the general population as a control group. Written consent was obtained followed by detailed medical, personal history, and systemic examination. Patients with known kidney disease were excluded from the study.

The following anthropometric parameters were studied: (i) Age: Was recorded from birthday by calendar to the nearest of year (<6 and >6 months), (ii) height: It was measured in cm, with the help of height measurement stadiometer, (iii) body weight: It was measured in kg, by portable human weighing machine, and (iv) body mass index (BMI): It was calculated by the formula: BMI = Weight (in kg)/height (m^2).

The biochemical parameters were estimated in the clinical biochemistry laboratory using commercial kits adapted to auto analyzer. Blood samples from subjects and controls were collected in ethylenediamine tetraacetic acid bulb in all the diabetic patients for investigation of fasting and post-meal plasma glucose. Estimation of serum glucose was carried out by glucose oxidase and peroxidase method.[4] Serum was separated from blood by centrifugation at 3000 rpm for 10 min. Serum urea was estimated by Berthelot's method[5] while creatinine was estimated by alkaline Jaffe's Picrate method.[6] These biochemical parameters were determined by using a fully automated clinical chemistry analyzer. The normal levels of creatinine were considered 0.8-1.4 mg/dL and for urea 10-45 mg/dL.[7] HbA1c of all subjects in the study was estimated by ion exchange resin method using the diagnostic HbA1c kits of Asritha Diatech as per the guidelines provided.[8] Mean ± standard deviation (SD) were calculated. As two independent parameters were to be tested in three population groups-control, Type 1 diabetics, Type 2 diabetics, one-way analysis of variance test was used for statistical analysis. Correlations of serum creatinine, serum urea levels with HbA1c and duration of illness in diabetic patients were analyzed by applying Pearson's coefficient correlation.

RESULTS

Anthropometric measurements in non-diabetic subjects (control group), Type 1 diabetics/insulin dependent diabetes (IDDM) and Type 2 diabetics/non-IDDM (NIDDM) were recorded in Table 1 in mean ± SD. There was no significant difference in the age, height, weight, and BSA in subjects in the three groups.

Table 2 indicates mean ± SD of fasting and post-meal blood sugar (FBS and PBS) levels and HbA1c levels in the control, Type 1 diabetes and Type 2 diabetes group. There was a significant increase in FBS and PBS levels in both Type 1 and Type 2 diabetics as compared to control group. HbA1c levels were significantly higher in both Type 1 and Type 2 diabetics as compared to control group, values being higher in Type 1 diabetics as compared to those with Type 2 diabetes group.

Table 3 shows mean ± SD of the levels of serum creatinine and urea in non-diabetic (control), Type 1 diabetics and Type 2 diabetics. There was statistically significant increase in levels of both serum creatinine and urea in both the diabetic groups as compared to control group.

Table 4 shows the correlation of serum urea and creatinine with HbA1c and duration of diabetes in IDDM/Type 1 diabetes group and NIDDM/Type 2 diabetics group by Pearson's coefficient correlation. There was association of serum urea and creatinine in Type 1 diabetic group with HbA1c level and duration of diabetes but not Type 2 diabetic group (Figures 1-4).

DISCUSSION

Diabetes mellitus is a major cause of morbidity and mortality. Diabetic nephropathy is the kidney disease that occurs as a result of diabetes. An international study has reported that diabetes control worsened with longer duration of the disease, with neuropathy as the most common complication followed by cardiovascular complications, renal complications, retinopathy, and foot ulcers.

Diabetic nephropathy can occur in both Type 1 and Type 2 diabetes mellitus.[9] The incidence and pathology of

Table 1: Comparison among study groups for anthropometric parameters

Parameters	Groups	N	Mean±SD	Median	IQR	One-way ANOVA test	
						F value	*P* value
Age (years)	Control	72	48.10±5.62	48.00	10.00	1.495	0.227
	NIDDM	72	48.54±4.78	48.00	8.00		
	IDDM	72	47.01±5.89	45.00	10.00		
Height (cm)	Control	72	162.57±6.38	163.00	7.00	0.795	0.453
	NIDDM	72	162.11±5.94	162.00	9.00		
	IDDM	72	161.21±7.37	162.00	9.75		
Weight (kg)	Control	72	56.54±4.77	56.00	6.75	1.603	0.204
	NIDDM	72	56.07±6.99	56.00	8.00		
	IDDM	72	54.86±5.44	55.00	6.75		
BMI (kg/m^2)	Control	72	21.64±2.27	21.19	3.56	2.500	0.084
	NIDDM	72	21.65±3.30	21.66	4.48		
	IDDM	72	20.74±2.78	20.52	3.54		

ANOVA: Analysis of variance, IDDM: Insulin dependent diabetes, NIDDM: Non-insulin dependent diabetes, BMI: Body mass index, SD: Standard deviation, IQR: Inter quartile range

Table 2: Comparison among study groups for FBS, PBS levels and HbA1c

Parameters	Groups	Mean±SD	Median	IQR	One-way ANOVA test	
					F value	*P* value
FBS (mg/dL)	Control	83.79±6.50	86.00	6.00	46.295	0.000*
	NIDDM	97.54±11.50	96.00	12.00		
	IDDM	87.58±7.80	88.00	7.50		
PBS (mg/dL)	Control	127.93±9.85	128.00	9.00	126.198	0.000*
	NIDDM	171.42±14.60	172.00	25.00		
	IDDM	162.85±24.45	169.50	49.00		
HbA1c (%)	Control	5.11±0.30	5.10	0.48	3.407	0.035*
	NIDDM	6.62±0.03	5.80	0.60		
	IDDM	5.98±0.32	5.90	0.58		

*P<0.005: Statistical significant difference, FBS and PBS: Fasting and post-meal blood sugar, HbA1c: Glycosylated hemoglobin, SD: Standard deviation, ANOVA: Analysis of variance, IQR: Inter quartile range

Table 3: Comparison among study for serum creatinine and serum urea

Parameters	Groups	Mean±SD	Median	IQR	One-way ANOVA test	
					F value	*P* value
Serum urea (mg/dL)	Control	27.22±2.94	27.00	2.00	33.499	0.000*
	NIDDM	31.13±3.10	31.00	5.00		
	IDDM	31.00±3.67	32.00	6.00		
Serum creatinine (mg/dL)	Control	1.03±0.19	1.10	0.28	50.965	0.000
	NIDDM	1.28±0.16	1.30	0.20		
	IDDM	1.31±0.19	1.30	0.10		

*P<0.005: Statistical significant difference, SD: Standard deviation, IDDM: Insulin dependent diabetes, NIDDM: Non-insulin dependent diabetes, ANOVA: Analysis of variance, IQR: Inter quartile range

nephropathy vary in both types of diabetes.[10] Although the overall incidence of nephropathy was considered to be substantially higher in Type 1,[11] more recent data suggest that the renal risk is equivalent in both diabetes.[12] Although there have been studies on microalbuminuria, serum creatinine and urea levels in Type 2 diabetes mellitus, comparative studies for the same, in Type 1 and Type 2 diabetes mellitus has hardly been reported. Many studies have reported nephropathy as a complication due to the long standing duration of diabetes and correlated it with microalbuminuria, hypertension, but there are few studies which have correlated levels of serum creatinine and urea,

Table 4: Correlation of study parameters with duration of diabetes and HbA1c

NIDDM	Duration			HbA1c		
	Pearson correlation	***P* value**	**Correlation**	**Pearson correlation**	***P* value**	**Correlation**
Duration				−0.122	0.307	Not significant
HbA1c	−0.122	0.307	Not significant			
Serum creatinine	−0.033	0.783	Not significant	0.093	0.438	Not significant
Serum urea	0.096	0.420	Not significant	0.118	0.325	Not significant
IDDM	**Duration**			**HbA1c**		
	Pearson correlation	***P* value**	**Correlation**	**Pearson correlation**	***P* value**	**Correlation**
Duration				0.716	0.000	Significant
HbA1c	0.716	0.000	Significant			
Serum creatinine	0.196	0.099	Not significant	0.275	0.019	Significant
Serum urea	0.197	0.096	Not significant	0.282	0.016	Significant

NIDDM: Non-insulin dependent diabetes, HbA1c: Glycosylated hemoglobin

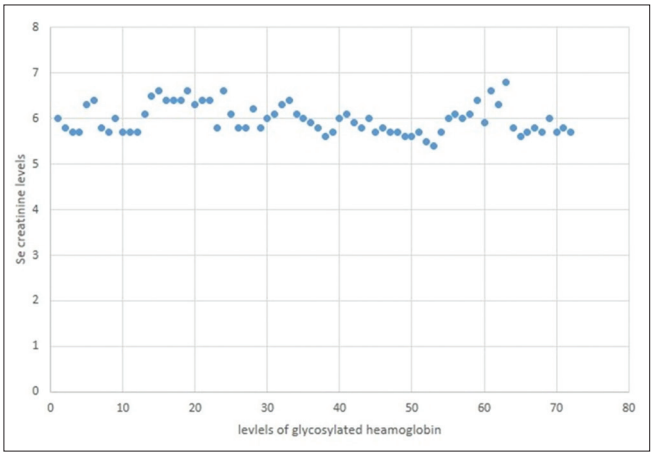

Figure 1: Correlation of serum creatinine levels with glycosylated hemoglobin in Type 1 diabetes mellitus

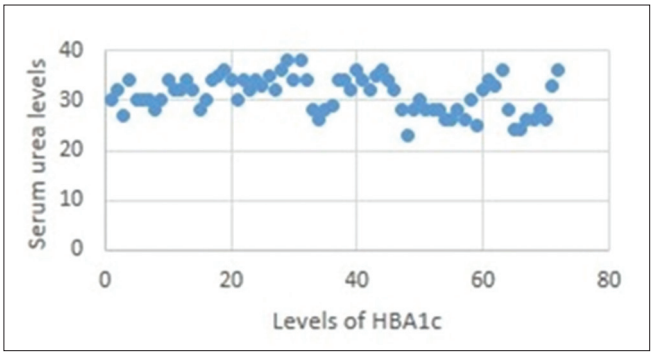

Figure 2: Correlation of serum urea levels with glycosylated hemoglobin in Type 1 diabetes mellitus

(which are markers for GFR) with duration of diabetes and glycemic index (HbA1c levels).[12-14] The exact cause of diabetic nephropathy is unknown, but various postulated mechanisms are hyperglycemia, advanced glycation products and activation of cytokines. Although it has been stated by various authors that poor glycemic status is one of the key factors responsible for diabetic nephropathy, there is scarce data available on the correlation of serum urea and creatinine levels with the glycemic status (HbA1c levels) in diabetic population. This study was undertaken to study the levels of serum creatinine and urea in Type 1 and Type 2 diabetes mellitus and further study their correlation with duration of diabetes and HbA1c levels.

Nephropathy is the leading cause of chronic renal failure worldwide and also in India which is responsible for renal failure in about one-third of patients who undergo dialysis. Thus, if there could be early detection of diabetic nephropathy with simple tests, it could be helpful in timely intervention with particular attention to glycemic control. Simple biomarker tests like serum creatinine and urea along with estimation of HbA1c would, particularly benefit the diabetic patients with poor socioeconomic status.

Hyperglycemia (poor glycemic control) is a characteristic feature of diabetes mellitus, is a fact well accepted by many.[15] In this study, there was a statistical significant increase in serum creatinine and urea levels in Type 1 and Type 2 diabetic study group as compared to the healthy control subjects with levels being higher in Type 1 diabetic population as compared to Type 2 diabetic subjects.

There was an increase in level of fasting, post-meal blood glucose and HbA1c levels in both Type 1 and Type 2 diabetic patients when compared with healthy controls, with levels being higher in Type 1 diabetic study group as compared to Type 2 diabetic study group. The duration of diabetes in Type 1 and Type 2 diabetics was 7.32 ± 1.52 and 2.47 ± 1.82, respectively. The duration of diabetes and HbA1c was higher in Type 1 diabetic subjects as compared to Type 2 diabetics. The previous studies done by various investigators have reported increase in levels of serum creatinine and urea in diabetic population.[16-18]

The levels of serum creatinine and urea when correlated with the duration of diabetes and HbA1c levels by Pearson's correlation coefficient, in our study showed correlation of serum urea and

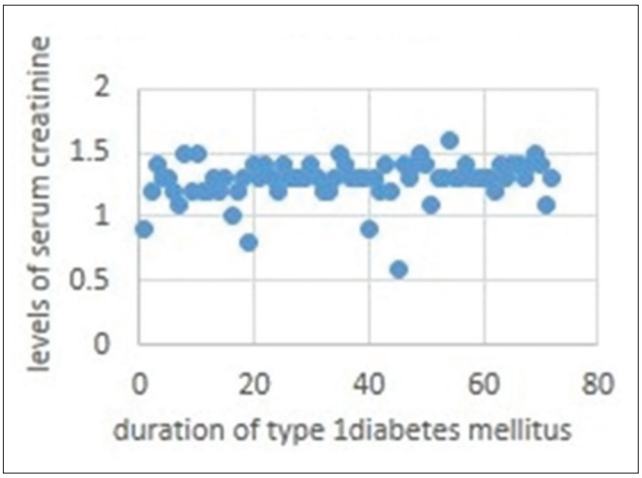

Figure 3: Correlation of serum creatinine levels with duration of diabetes in Type 1 diabetes mellitus

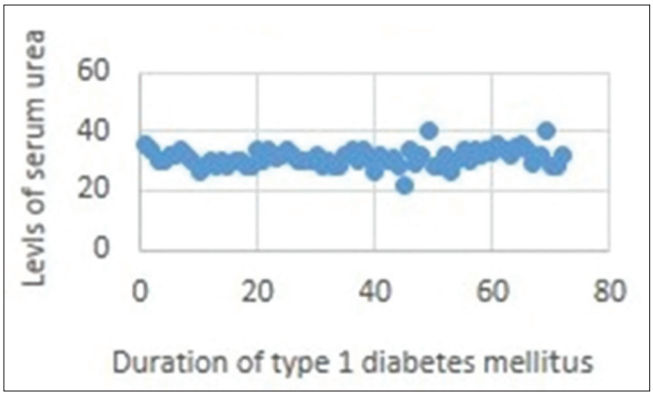

Figure 4: Correlation of serum urea levels with duration of diabetes in Type 1 diabetes mellitus

creatinine with HbA1c in Type 1 diabetes subjects but not in Type 2 diabetics/NIDDM group. There was no correlation of serum creatinine and urea levels with duration of diabetes in Type 2 diabetics. This may be due to the fact that the duration of illness in Type 2 diabetes (2.47 ± 1.82 years) was brief as compared to Type 1 diabetes mellitus. Also in Type 1 diabetes, hyperglycemia starts in the early decades of life with acute deficiency of insulin from the start of disorder and may be considered as the recognized cause of nephropathy. On the contrary in Type 2, hyperglycemia starts after the age of forty usually when the kidneys have already suffered the long-term consequences of ageing and other promoters of chronic renal injury such as arterial hypertension, dyslipidemia, obesity. This probably might be cause for increased levels of serum creatinine and urea in Type 2 diabetics but not correlating with duration of diabetes in Type 2 diabetes mellitus. Unnikrishnan et al. in his study in the Indian diabetic population had observed that poor glycemic control is a key factor which is responsible, for micro- and macrovascular changes that occur in diabetes, predisposing diabetic patients to complications.[19] Mohan et al. in his study had reported that although there is scarce data on the prevalence on diabetic complications in India, there is increase in number of early-onset diabetes cases which is also responsible for various diabetic complications due to longer disease duration.[18] Hyperglycemia may directly cause mesangial expansion and injury by increasing the mesangial cell glucose concentration. Initially, glomerular mesangium expands by cell proliferation and later by cell hypertrophy. Transforming growth factor β (TGF-β) is important in the mediation of expansion and later fibrosis by the stimulation of collagen and fibronectin.[20,21] Glucose can bind reversibly and finally irreversibly to proteins in the kidneys and circulation to form AGEs. Due to long standing hyperglycemia, AGEs can form complex cross-links over years and contribute to renal damage. Furthermore, TGF-β, platelet-derived growth factor and vascular endothelial growth factor are elevated in diabetic nephropathy thereby acting as mediators of proliferation and expansion, contributing to further renal and microvascular complications.[22]

Studies in experimental animals suggest that the diabetic state is associated with impaired renal autoregulation. As a result, increase in systemic pressure does not produce expected afferent arteriolar vasoconstriction that would minimize transmission of the elevated pressure to the glomerulus. Why this occurs is not clear, but increased production of vasodilator prostaglandins appears to be involved.

The reduced filtering capacity of the kidney in Type 1 and Type 2 diabetic patients would lead to accumulation of waste products and thereby increase in serum creatinine and urea levels.[23] Impaired function of the nephron in diabetic patients causes high serum creatinine level.[24]

Longer duration of diabetes would amount to hyperglycemia lingering for a long time and hence its potential hazards where the excess glucose combines with collagen, tissue proteins leading to its non-enzymatic glycosylation resulting in microvascular and macrovascular damage. As hyperglycemia leads to non-enzymatic glycosylation, in a similar manner hemoglobin is also one of the proteins that undergoes irreversible glycosylation. Although this process does not contribute to microvascular disease, it is useful clinically since the HbA1c level is usually a reasonably accurate estimate of long-term hyperglycemia. Thus, there exists every possibility of existence of linear relation between hyperglycemia resulting in high levels of HbA1c and formation of irreversible AGEs via an Amadori rearrangement which can contribute to the associated renal and microvascular complications. Mishra et al. in study on diabetic subjects reported that serum urea and serum creatinine in diabetic patients were significantly increased with increasing duration of diabetes and thereby concluded that increase in duration of diabetes was the risk factor for the kidney damage progression.[25] Over a time high blood sugar level damage millions of nephron, the tiny filtering units in each kidney.[26] An increase in serum creatinine and serum urea occurs when there is damage to the kidney or it is not functioning properly. This increase in the blood sugar levels might lead to renal dysfunction. If the kidneys are unable to function normally, the serum

creatinine would not be cleared by the kidneys and would increase abnormally. The elevated levels of HbA1c can be lowered by intensive treatment plan, but the elevated levels of serum urea and creatinine which are set on increase due to permanent damage to the kidneys would be difficult to reverse because damage to the kidneys in diabetes mellitus is a permanent phenomenon. The elevated levels of serum urea and creatinine are the measures of glomerular damage which can, in no way be reversed by intensive treatment plan. The only way to control this progressive glomerular damage and thereby elevated levels of serum and creatinine web would be early detection and intervention.

CONCLUSION

Linear relationship of serum creatinine and urea level was found with increased levels of HbA1c in Type 1 diabetic subjects. To monitor the diabetes patients, estimation of blood urea and creatinine level along with HbA1c level is highly recommended. Serum urea and creatinine are simple and useful biomarkers which can serve as predictor tests for assessing kidney functions (nephropathy) in diabetic patients.

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