Print ISSN: 2321-6379
Online ISSN: 2321-595X
DOI: 10.17354/ijss/2017/85

Original Article

Plasma Cystatin C as Marker of Early Renal Impairment in Diabetes Mellitus

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Abstract

Background: The presence of microalbuminuria, which is detected at the time of diagnosis of Type 2 diabetes, has been attributed to the hyperglycemia itself and may reverse to normoalbuminuria after adequate glycemic control. However, microalbuminuria, particularly if it is persistent may also represent incipient nephropathy. Cystatin C is freely filtered by glomerulus.

Materials and Methods: This study has been conducted at a tertiary care hospital with 60 subjects from both inpatient as well as outpatient (diabetes clinic) departments have been selected. The Institutions Ethics Committee has approved the study. Informed consent was obtained from all the study participants. 60 study subjects have been selected and categorized into three groups: (1) Non-diabetic subjects with normoalbuminuria (*n* = 20), (2) Diabetic patients with normoalbuminuria (<30 mg/day of albumin) and normal plasma creatinine (<1.2 mg/dl) (*n*=20), (3) Diabetic patients with microalbuminuria (30-300 mg/day of albumin) and moderately raised plasma creatinine (1.2-1.8 mg/dl) (*n* =20).

Result: The mean cystatin C values in Group B were 1 ± 0.31 and in Group C were 1.08 ± 0.24. In Group B, 60% of patients had raised cystatin C levels whereas in Group C 16 patients (i.e., 80%) had raised cystatin C levels. When plotted against serum creatinine levels, it is evident that in Group B small majority of patients have raised cystatin C inspite of normal serum creatinine levels and in Group C around 80% of patients have it raised. This indicates that cystatin C is a better marker of early diabetic nephropathy when compared with serum creatinine levels.

Conclusion: Cystatin C is an early and better marker of incipient diabetic nephropathy in Type 2 diabetics when compared with serum creatinine. Serum cystatin C is also independent and early maker of incipient diabetics nephropathy and even when compared to microalbuminuria in Type 2 diabetic patients.

Key words: Creatinine, Diabetes mellitus, Diabetic nephropathy, Microalbuminuria, Plasma cystatin C

INTRODUCTION

Diabetes is an emerging global health problem. It has now reached epidemic proportions with a current prevalence of about 170 million. India has the highest prevalence of diabetes in the world. The problem of diabetes and its complications is the price that is being paid for an increase in life expectancy with a concomitant increase in dietary affluence and a decrease in physical activity. The human impact of diabetes includes devastating complications such as retinopathy, neuropathy, and nephropathy with a lot of the most productive years of life. Nowadays, diabete gras (as described by the French Diabetologist Etienne Lancereaux), i.e., Type 2 diabetes mellitus (DM) accounts for 95% of all cases of diabetes worldwide while in comparison diabete maigre, i.e., Type 1 DM is seen less often.[1,2]

It is not common to find evidence of microvascular complications of diabetes in newly diagnosed Type 2 diabetic patients. Proteinuria has been reported in up to 50% of patients with Type 2 diabetes, and in many patients, it is seen soon after diagnosis. The presence of microalbuminuria, which is detected at the time of diagnosis of Type 2 diabetes, has been attributed to the hyperglycemia itself and may reverse

Access this article online

www.ijss-sn.com

Month of Submission : 01-2017
Month of Peer Review : 02-2017
Month of Acceptance : 02-2017
Month of Publishing : 03-2017

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to normoalbuminuria after adequate glycemic control. However, microalbuminuria, particularly if it is persistent may also represent incipient nephropathy.

The presence of microalbumin in the urine heralds the onset of kidney disease in diabetics. It is not known whether it indicates a greater risk for kidney disease in patients without diabetes. The presence of microalbumin indicates early damage to the glomerular blood vessels; however, in diabetes it also could indicate failure of renal auto regulation. Although there is no direct clinical evidence to support this theory, microalbuminuria is evidence of generalized of vascular function.[3,4]

In the last 40 years, plasma creatinine has become the most commonly used endogenous marker of renal function. Its rate of appearance in the bloodstream is related to muscle mass, so that intra-individual concentrations are affected by age and gender.

Cystatin C is a 122 - amino acid, 13 kDa protein that is a member of the family of cysteine proteinase inhibitors. It is the product of a "housekeeping" gene expressed in all nucleated cells and is produced at a constant rate.[4] Due to its small size and basic pH (~9.0), cystatin C is freely filtered by glomerulus. Cystatin C does not return to the blood stream and is not secreted by renal tubules, it has been suggested to be closer to the "ideal" endogenous marker.[5,6]

Aims and Objectives of the Study

To determine whether plasma cystatin C is a marker of early renal impairment when compared with microalbuminuria in Type 2 diabetic subjects with normal plasma creatinine (<1.2 mg/dl) and moderately elevated plasma creatinine (1.2-1.8 mg/dl).

MATERIALS AND METHODS

This study has been conducted at a tertiary care hospital with 60 subjects from both inpatient as well as outpatient (diabetes clinic) departments have been selected. The Institutions Ethics Committee has approved the study. Informed consent was obtained from all the study participants.

60 study subjects have been selected and categorized into three groups:

1. Non-diabetic subjects with normoalbuminuria ($n = 20$)
2. Diabetic patients with normoalbuminuria (<30 mg/day of albumin) and normal plasma creatinine (<1.2 mg/dl) ($n = 20$)
3. Diabetic patients with microalbuminuria (30-300 mg/day of albumin) and moderately raised plasma creatinine (1.2-1.8 mg/dl) ($n = 20$).

Blood pressure (BP) has been measured in all subjects in sitting position on the right arm with a standard mercury sphygmomanometer. Mean values have been determined from two independent measurements taken at 5 min intervals.

Blood samples have been collected to determine fasting plasma glucose, postprandial plasma glucose or 2 h post glucose and these have been determined by glucose oxidase method in a dry chemistry analyzer, Vitros 250. Glycosyl and hemoglobin (Hb) levels have been measured by chromatography base high-performance liquid chromatography assay and expressed as a percentage. Urine sugar and urine ketones have been checked by dipstick method.

Plasma cystatin C has been measured by immunonephelometry. Normal values considered were between 0.52 and 0.98 mg/L. Microalbuminuria has been determined by an immunotubidimetric method from Siemens Diagnostics, in urine collected over 24 h and expressed as mg/24 h. Plasma creatinine has been determined using Jaffe's method and expressed as mg/dl.

In all the above cases, for exclusion of the diseases, enlisted, mostly we had to resort to clinical examination, urine examination, blood urea nitrogen, serum creatinine, T3, T4 and thyroid-stimulating hormone (to rule out thyroid disorders), serum bilirubin, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, alkaline phosphatase, ultrasonography of abdomen (for jaundice or any liver disease).

RESULTS

A total of 60 subjects were studied. They were divided equally into three groups; Group A consisted of 20 control subjects, i.e., the non-diabetic patients, Group B consisted of 20 diabetic subjects with normal serum creatinine (<1.2 mg/dl) and Group C consisted of 20 diabetic subjects with moderately elevated serum creatinine (1.2-1.8 mg/dl). The results of the various clinical and biochemical parameters and their interrelationship are as follows.

- Group A had a mean age of 59.9 years with the range being 49-70 years
- Group B had a mean age of 59.3 years with a standard deviation of 8.92 years, and all subjects were within the range of 47-74 years
- Group C had a mean age of 62 years with a standard deviation of 8.09 years, and all subjects were within the range of 48-73 years (Table 1).

In Group B almost half the patients lie in the <10 set and the other half lie in the 11-20 years set. In Group C,

however, only 2 patients belong to the first set (<10 years) and the remaining belong to the 11-20 years set with majority among them suffering from diabetes for over 15 years (Table 2).

The number of male patients of Type 2 diabetes is more than females. There are 15 diabetic males and 5 diabetic females in Group B and 12 diabetic males and 8 diabetic females in Group C (Table 3).

- Group A shows a mean fasting blood sugar (FBS) value of 91.85 with a standard deviation of 5.69
- Group B shows a mean FBS value of 117.45 with a standard deviation of 13.38
- Group C shows a mean FBS value of 127.05 with a standard deviation of 18.05.

When compared they show a statistically significant *P* value of 0.001 and 0.01 (Table 4).

- Group A shows a mean post lunch blood sugar (PLBS) value of 116.15 with a standard deviation of 16.24
- Group B shows a mean PLBS value of 163.85 with a standard deviation of 23.10
- Group C shows a mean PLBS value of 195.15 with a standard deviation of 28.91.

When compared they show a statistically significant *P* value of 0.033 and 0.002 and 0.04 (Table 5).

- Group A shows a mean HbA_1c value of 5.56 with a standard deviation of 0.44
- Group B shows a mean HbA_1c value of 7.32 with a standard deviation of 0.48
- Group C shows a mean HbA_1c value of 7.62 with a standard deviation of 0.54.

When compared they show a statistically significant *P* value of 0.029 and 0.011 (Table 6).

In Table 7 we can see that the mean BP in Group A is 120/80 mm of Hg with a standard deviation of 6.88 and 4.55 for systolic and diastolic BP, respectively.

In Group B the mean BP seen is 128/82 mm of Hg with a standard deviation of 11.72 and 8.14 for systolic and diastolic BP, respectively.

And in Group C the mean BP is 142/90 mm of Hg with a standard deviation of 15.20 and 7.69 for systolic and BP, respectively.

Figure 1 compares the mean systolic and diastolic BP in all three groups. It shows that in Group A and B the values are within the normal range whereas in Group C the mean BP has gone beyond 140/90 mm of Hg.

- Group A has microalbuminuria absent

Table 1: Age distribution

Age (years)	Group A	Group B	Group C
<50 years	1 (5)	6 (30)	2 (10)
51-60 years	11 (55)	6 (30)	7 (35)
61-70 years	8 (40)	5 (25)	7 (35)
≥71 years	0	3 (15)	4 (20)
Mean±standard deviation	59.9±5.84	59.3±8.92	62±8.09
Range	49-70	47-74	48-73

Table 2: Duration of DM

Duration of DM (years)	Group B	Group C
<10	9	2
11-15	5	5
16-20	6	13

DM: Diabetes mellitus

Table 3: Sex distribution

Gender	Group A	Group B	Group C
Male	12	15	12
Female	8	5	8

Table 4: Observations of blood sugar levels

FBS	Group A	Group B	Group C
Mean	91.85	117.45	127.05
Median	93.0	117.5	125.5
Standard deviation	5.69	13.38	18.05
Range	81-100	100-147	102-173
P value (A and B)	0.001		
P value (A and C)	0.01		

One-way ANOVA (Tukey's test). FBS: Fasting blood sugar

Table 5: PLBS

PLBS	Group A	Group B	Group C
Mean	116.15	163.85	195.15
Median	119	165	194.61
Standard deviation	16.24	23.10	28.91
Range	78-140	124-220	150-250
P value (A and B)	0.033		
P value (A and C)	0.02		
P value (B and C)	0.04		

One-way ANOVA (Tukey's test). PLBS: Post lunch blood sugar

Table 6: HbA_1c

HbA_1c	Group A	Group B	Group C
Mean	5.56	7.32	7.62
Median	5.50	7.40	7.75
Standard deviation	0.44	0.48	0.54
Range	4.6-6.5	6.5-8.1	6.9-8.9
P value (A and B)	0.029		
P value (A and C)	0.011		

One-way ANOVA (Tukey's test). HbA_1c: Hemoglobin A_1c

- Group B shows a mean microalbuminuria level of 161.6 with a standard deviation of 53.13
- Group C shows a mean microalbuminuria level of 206 with a standard deviation of 54.36.

Comparison between groups shows a statistically significant $P = 0.01$ (Table 8).

- Group A shows a mean cystatin C level of 0.60 with a standard deviation of 0.04
- Group B shows a mean cystatin C level of 1.00 with a standard deviation of 0.31
- Group C shows a mean cystatin C level of 1.08 with a standard deviation of 0.24.

Comparison between groups shows a statistically significant $P = 0.001$ and 0.01 and 0.04 (Table 9).

In Group B there are 12 patients with presence of microalbumin in urine, whereas in Group C all the 20 patients have it present. On the other hand, cystatin C is raised in 13 patients in Group B and in 16 patients in Group C (Table 10).

DISCUSSION

Diabetes is an emerging health problem in developed as well as developing countries. India has the highest prevalence of diabetes in the world. It has gained much popularity due to its various microvascular and macrovascular complications. As diabetes is an independent risk factor for cardiovascular and cerebrovascular disease, the early detection of diabetes and its complications is of utmost importance.[7,8]

Once of the most important microvascular complications of diabetes are diabetic nephropathy. Diabetic nephropathy is the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy and is associated with hypertension and a high risk of cardiovascular morbidity and mortality.

The presence of microalbuminuria is a known complication in patients of diabetes. It is an early sign that before glomerular filtration rate (GFR) deteriorates. In Type 2 diabetes, the incidence of microalbuminuria is around 2.0% per year and the prevalence at 10 years after diagnosis is around 25%. Although a reliable investigation, collection of urine over 24 h and other factors (i.e.,: Short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure, and acute febrile illness) influencing its presence makes testing for microalbuminuria a very tedious job.[9,10]

Cystatin C is a small 13 kDa protein, that is a member of the cysteine proteinase inhibitor family that is produced at a constant rate by all nucleated cells. Due to its small size it is freely filtered by the glomerulus, and is not secreted but

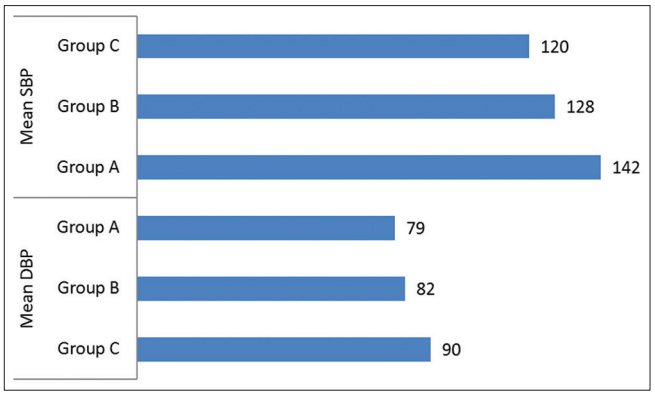

Figure 1: Blood pressure comparison

Table 7: BP and diabetic nephropathy

Parameter	Group A	Group B	Group C
Systolic BP			
Mean	120	128	142
Median	120	129	140
Standard deviation	6.88	11.72	15.20
Range	110-130	110-150	120-162
Diastolic BP			
Mean	79	82	90
Median	80	80	87
Standard deviation	4.55	8.14	7.69
Range	70-88	70-100	78-102

BP: Blood pressure

Table 8: Microalbuminuria and cystatin C

Microalbuminuria	Group A	Group B	Group C
Mean	Absent	161.6	206
Median		162	213
Standard deviation		53.13	54.39
Range		99-162	108-288
P value (B and C)	0.01		

Chi-square test.

Table 9: Cystatin C

Cystatin C	Group A	Group B	Group C
Mean	0.60	1.00	1.08
Median	0.59	1.06	1.12
Standard deviation	0.04	0.31	0.24
Range	0.52-0.67	0.54-1.46	0.52-1.4
P value (A and B)	0.001		
P value (A and C)	0.01		
P value (B and C)	0.04		

One-way ANOVA (Tukey's test)

Table 10: Microalbuminuria and cystatin C present

Parameter	Microalbuminuria present	Cystatin C present
Group B	12	13
Group C	20	16

is fully reabsorbed and broken down by the renal tubules. This means the primary determinate of blood cystatin C levels is the rate at which it is filtered at the glomerulus making it an excellent GFR marker. Estimation of serum cystatin C levels can be done on outpatient department (OPD) basis by a simple blood draw. As microalbuminuria is the first sign of renal microalbuminuria is an important factor in deciding on the usefulness of this test for patients with incipient diabetic nephropathy.[11,12]

60 patients with Type 2 diabetes either attending the OPD or admitted to hospital were included in our study. A detailed history with special importance to a number of years of diabetes and other comorbidities were taken. A complete clinical examination and required investigations according to the pro forma were done. They were divided equally into three groups. Groups A consisted of 20 control subjects, i.e., the non-diabetic patients, Group B consisted of 20 diabetic subjects with normal serum creatinine, and Group C consisted of 20 diabetic subjects with moderately elevated serum creatinine (1.0-1.8 mg/dl).[13-15]

In the study, in Group B the mean age of subjects was 55 years ± 7.9, whereas in Group C the mean age was 56 years ± 6.27. In Group B and C a majority of the patients are in the 50-70 years age group. In both these groups, there were more males than females (15 in Group B and 12 in Group C). For Group B, 60% of patients have had history diabetes for between 10 and 20 years. Whereas, in Group C 85% patients have had a history of diabetes between 10 and 20 years. Thus, our study shows that the prevalence of diabetes in more among the age group 50-70 years. The onset of diabetes is now earlier as majority of subjects in our study has onset of diabetes between 45 and 55 years. More males had diabetes than females and the incidence of microvascular changes in the kidneys was more with a history of the duration of diabetes between 10 and 20 years.

Al-Wakeel *et al.* showed that the peak incidence of diabetic nephropathy was present between 50 and 70 years if age. The mean age of the onset of diabetes is early, and the majority have diabetes in their forties. Studies conducted by Ericksson *et al.*, Pan *et al.*, Williams *et al.*, and Kanaya *et al.* show that males are more prone to develop diabetes than females. Evidence of a link between development and progression of diabetic nephropathy and duration of diabetes in Type 2 diabetes was clearly demonstrated in the UKPDS. Following diagnosis, progression to microalbuminuria occurred at 2.0% per year, from microalbuminuria to macroalbuminuria at 2.8% per year, and from macroalbuminuria to elevated plasma creatinine or renal replacement therapy at 2.3% per year. 10 years following diagnosis, microalbuminuria or worse diabetic nephropathy was present in 24.9% of patients.

Our study shows that in Group B the number of patients with presence of microalbuminuria in urine was 12 whereas in Group C all 20 patients had it present. Where microalbuminuria is plotted against serum creatinine levels, microalbuminuria values for certain patients in Group B rise inspite of normal creatinine, whereas in Group C where creatinine is raised to between 1.2 and 1.8 mg/dl, all patients have microalbuminuria present. This indicates that microalbuminuria is indeed an early marker of diabetic nephropathy as compared to serum creatinine levels. Various other studies have also shown that presence of microalbuminuria is an early indicator of diabetic nephropathy. de Zeeuw *et al.* while working on the RENAAL study showed that albuminuria is the most critical baseline predicator for end-stage renal disease. Chiarelli *et al.* showed that microalbuminuria is and an early sign that appears before GFR (derived using creatinine-based Cockcroft-Gault equation) deteriorates. Mogensen *et al.* and Keane *et al.* also showed that proteinuria was the strongest and most consistent marker for diabetic nephropathy. Date from the UKPDS demonstrated that approximately 25% of patients with Type 2 diabetes develop microalbuminuria or worse, diabetic nephropathy by 10 years. It is estimated that almost 50% of patients who develop microalbuminuria do so within 19 years from diagnosis of diabetes. From any stage of diabetic nephropathy, the rate of deterioration to the next stage is 2-3% per year.

The mean cystatin C values in Group B were 1 ± 0.31 and in Group C were 1.08 ± 0.24. In Group B, 60% of patients had raised cystatin C levels whereas in Group C 16 patients (i.e., 80%) had raised cystatin C levels. When plotted against serum creatinine levels, it is evident that in Group B small majority of patients have raised cystatin C inspite of normal serum creatinine levels and in Group C around 80% of patients have it raised. This indicates that cystatin C is a better marker of early diabetic nephropathy when compared with serum creatinine levels. This is in concurrence with other studies. Newman *et al.* and Nelsson *et al.* showed that cystatin C now can be widely used and can replace creatinine for the assessment of GFR in clinical practice. Dharnidharka *et al.* and Roos *et al.* have concluded that serum cystatin C is superior to serum creatinine as a marker of kidney function.

Where microalbuminuria is plotted against serum cystatin C levels for Group B and C, it can be seen that cystatin C rise in the same patients in whom the microalbuminuria is present. This indicates that when compared with microalbuminuria, cystatin C is also and early marker of incipient renal damage in Type 2 diabetes. Shani Shastri

et al. showed that cystatin C and microalbuminuria are independent risk factors for incipient CKD and could be useful as screening tools to identify those at increased risk. A. Piwowar *et al.* proved that cystatin C showed a significant increase in diabetic patients with microalbuminuria. Their study suggests that the determination of the plasma concentration of cystatin C is useful in the detection of incipient nephropathy in patients with non-insulin-dependent DM and is a better marker than creatinine.

The FBS levels were 91.85 ± 5.69 mg/dl (mean and standard deviation) in Group A subjects, 117.45 ± 13.38 mg/dl (mean and standard deviation) in Group B and 127.05 ± 18.05 mg/dl (mean and standard deviation) in Group C. The HbA_1c levels were 5.56 ± 0.44 in Group A, 7.32 ± 0.48 in Group B, and 7.62 ± 0.54 in Group C. This indicates a poorer control of sugar levels in diabetic subjects in Group B and even poorer glycemic control in the subjects with early diabetic nephropathy in Group C. Wilson *et al.* proved that those who showed evidence of renal damage, were found to have poor control of blood sugar levels. Landro *et al.* showed that a glycosylated Hb of more than 7.5% was a major risk factor for development of nephropathy.

The BP levels were within normal limits for the control group. In Group B, the BP levels were 128/82 mm of Hg ± 11.72/8.14, i.e., were still in normal limits. Whereas in Group C the BP was 142/90 ± 15.20/7.69. Most of the subjects in Group C were on antihypertensive medications. This shows that BP in patients with renal damage due to diabetes was on the higher side. Mogensen *et al.* showed the higher prevalence of hypertension in patients with established diabetic nephropathy and that antihypertensive treatment shows the decline in renal function in diabetic nephropathy. In another study, he also documented that elevated BP was very closely related to development of diabetic renal disease in Type 2 diabetic patients, moreover showed a correlation between BP and rate of progression.

Thus to summarize, it was necessary to study the correlation between microalbuminuria and cystatin C and in cystatin C is also an early marker of incipient renal damage in Type 2 diabetics. Tight control of blood sugars and BP is necessary to arrest the development of renal damage in Type 2 diabetes, and serum cystatin C levels may be used routinely or even as an alternative to microalbuminuria for the detection of diabetic nephropathy.

We may also remember that the incidence of diabetes and its complications are very high. In such small studies, it is hard to generalize or derive conclusive ideas regarding serious complications such as diabetic nephropathy. Thus, large-scale multi-centric studies are required for early detection of diabetic nephropathy and studying its correlation with serum cystatin C.

CONCLUSION

1. A higher prevalence of Type 2 DM is more in the 50-70 years age group and onset of diabetes has moved to forties
2. Prevalence of Type 2 DM is more than in females
3. Incidence of microvascular complications such as diabetic nephropathy increases when the duration of diabetes is more than 10 years
4. Hypertension often accompanies diabetics nephropathy
5. Poorer control of sugar levels is found in patients progressing toward diabetic nephropathy
6. Cystatin C is an early and better marker of incipient diabetic nephropathy in Type 2 diabetics when compared with serum creatinine
7. Serum cystatin C is also independent and early maker of incipient diabetics nephropathy and even when compared to microalbuminuria in Type 2 diabetic patients.

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How to cite this article: Shetty V, Jain HR, Singh G, Parekh S, Shetty S. Plasma Cystatin C as Marker of Early Renal Impairment in Diabetes Mellitus. Int J Sci Stud 2017;4(12):1-7.

Source of Support: Nil, **Conflict of Interest:** None declared.