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Original Research Article.

Serum Cystatin C as a Marker for Early Renal Impairment in Individuals with Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes and it is defined as a rise in the urinary albumin excretion rate and abnormal renal function. Some patient develop advanced renal impairment with normal urinary albumin level thus albuminuria is not the perfect marker for the early detection of Diabetic nephropathy. Cystatin C has been suggested one of such markers. The aim of this study was to examine the usefulness of cystatin C as an early marker of diabetic nephropathy.

Methods: It was a retrospective study to evaluate role of Cystatin C in Diabetic nephropathy. 52 patient's report from department of medicine in Hindu Rao Hospital, were analysed and compared with age related controls.

Results: Association was observed between increased levels of blood urea, serum creatinine and cystatin C with albuminuria. The association was statistically significant (p-value < .05). The significant sensitivity and specificity range for cystatin C was better as compared to blood urea and creatinine.

Conclusion: Cystatin C appears to be a better marker for detection of diabetic nephropathy in comparison to blood urea and serum creatinine.

Keywords: Albuminuria, Cystatin C, Marker, Diabetic Nephropathy, Blood Urea, Serum Creatinine.

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INTRODUCTION

Type 2 diabetes mellitus (DM) is a chronic metabolic disorder and its prevalence has been increasing steadily all over the world .Due to increasing trend, it is fast becoming an epidemic in some countries of the world with the number of people affected are expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare providers, especially in poorly developed countries. People living with type 2 DM are more vulnerable to various forms of both micro and macro vascular complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM. Progressive decline in renal function has been well described in patients with type 2 diabetes mellitus, but few studies have assessed the risk of acute renal failure in a large population of patients with type 2 diabetes. Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes and it is defined as a rise in the urinary albumin excretion rate and abnormal renal function.

Currently, changes in albuminuria are considered a hallmark of onset or progression of DN. However, some patients with diabetes have advanced renal pathological changes and progressive kidney function decline even if urinary albumin levels are in the normal range, indicating that albuminuria is not the perfect marker for the early detection of DN. Cystatin C has been suggested one of such markers.

Albuminuria, which is believed to reflect hemodynamic disturbances within the glomerulus, has long been identified as a major prognostic indicator in individuals with Diabetes. Impaired glomerular filtration rate (GFR), a complementary sign of kidney damage, is also associated with increased risk. As a result, screening for kidney disease using urinary albumin and serological markers of kidney function has become a cornerstone of diabetes care, facilitating targeted interventions to prevent Cardiovascular and kidney disease progression.

Konrad Walzak et al in their study concluded that serum Cystatin C seemed to be a promising marker in estimation of renal function

in early stages of diabetic kidney disease, when GFR is still normal or elevated. Though role in developed progressive nephropathy was less likely.[1] Ian H. DeBoer et al in their study concluded that the association of cystatin C–estimated GFR with mortality was modestly stronger than that for GFR estimated from serum creatinine.[2]

Lopez Gomez JM et al had observed that cystatin C can show vascular and renal damage in patients without urinary albumin.[3] Yung Kung Jeon et al in their study concluded that cystatin C measurement in urine and serum is a useful, practical, non-invasive tool for the evaluation of renal involvement in the course of diabetes, especially in normoalbuminuric patients.[4]

AIMS AND OBJECTIVES

Aim

To co-relate Cystatin C levels with diabetic nephropathy.

Objective

To study co-relation between cystatin C in patients of type 2 diabetes mellitus with serum creatinine, blood urea and albuminuria.

MATERIALS AND METHODS

It was a retrospective study to evaluate role of Cystatin C in Diabetic nephropathy. 52 patient's report were analysed and compared with age related controls. We did not view records of those who had history of renal transplant or were on Renal Replacement Therapy.

Investigations

1. Blood sugar fasting and Post prandial
2. Complete hemogram
3. LFT, KFT, Serum electrolytes.
4. Urine for albuminuria.
5. Serum cystatin C.
6. Ultrasound Abdomen and pelvis (if required).
7. HbA1C.

Cystatin C was measured by a particle-enhanced turbidimetric method and creatinine by an enzymatic method.

Statistical Analysis

Statistical analysis was done using SPSS 15.For calculating mean unpaired t-test and Mann Whitney test were used. For percentage Chi square/Fischer's test were used. p value was calculated. p-value < 0.05 was considered significant. ROC curve was plotted. Sensitivity and specificity were calculated.

RESULTS

A total of 52 patients with type 2 diabetes mellitus were studied. Results were compared with controls.

In our study-out of 52 patients,28 patients were female while 24 patients were male. Mean age of patients was 56.7 years. Diabetic nephropathy for study purpose was defined as presence of albuminuria in the patients. Mean HbA1C of patients was 7.7%.

Association was observed between increased levels of blood urea, serum creatinine and cystatin C with albuminuria. The association was statistically significant (p-value < .05).

Statistically significant association was not seen with glycaemic control (HbA1C).

Receiver operating characteristics curve was plotted. Area under the curve was significant for increased levels of blood urea, creatinine and cystatin C. However, area under the curve was more for cystatin C as compared to either of them. Also the significant sensitivity and specificity range for cystatin C was better as compared to blood urea and creatinine. Michele Mussap et al[5] in their study had reported similar observation.

Association with dyslipidaemia i.e with raised triglyceride levels was seen. The association might be due to pathophysiology of diabetes mellitus rather than direct association with nephropathy.

Table 1: Mean values of various parameters in cases and controls

	Diabetics		Controls		p-value
	Mean	± SD	Mean	± SD	
B.urea	43.92	38.18	42.73	25.27	0.455
Creat	1.37	1.67	1.33	0.81	0.466
CystatinC	1.35	1.00	1.13	0.49	0.208
U.Alb	16		3		0.207
TG	192.35	121.71	167.07	118.49	0.239
Chol	138.19	30.23	111.27	22.36	0.001
HDL	55.75	17.62	42.33	10.60	0.003
LDL	121.17	61.93	84.40	21.07	0.014

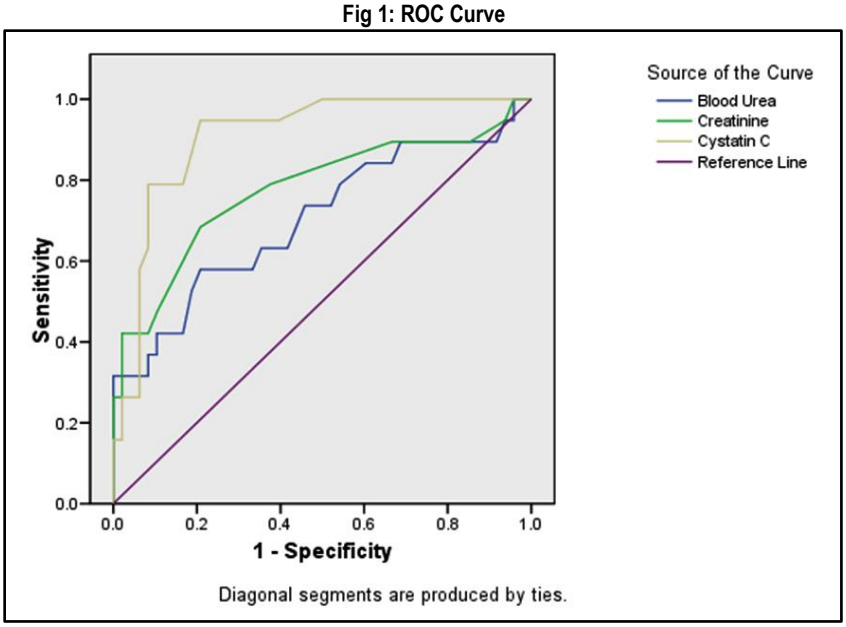
Table 2: Significance of kidney function test & lipid profile with albuminuria.

	Yes		No		p-value
	Mean	± SD	Mean	± SD	
B.urea	67.26	55.37	34.31	16.85	0.000
Creat	2.42	2.53	0.94	0.36	0.000
Cystatin C	2.12	1.28	0.97	0.41	0.000
TG	204.79	132.26	179.52	116.32	0.222
Chol	126.05	32.08	134.58	30.08	0.154
HDL	46.00	14.73	55.42	17.49	0.021
LDL	84.68	59.26	124.13	53.22	0.005

Table 3: Sensitivity and specificity values

Blood Urea			Creatinine		
Alb (Yes) if ≥	**Sensitivity**	**Specificity**	**Alb (Yes) if ≥**	**Sensitivity**	**Specificity**
10	100.00%	o.oo%	-0.9	100.00%	0.00%
12.5	100.00%	2.08%	0.35	100.00%	4.17%
14.5	100.00%	4.17%	0.65	94.74%	6.25%
15.5	94.74%	41.17%	0.75	89.47%	14.58%
16.5	94.74%	6.25%	0.85	89.74%	33.33%
17.5	89.47%	8.33%	0.95	78.95%	62.50%
19	89.47%	14.58%	1.05	68.42%	79.17%
20.5	89.47%	16.67%	1.15	47.37%	89.58%
21.5	89.47%	18.75%	1.25	42.11%	91.67%
22.5	89.47%	27.08%	1.35	42.11%	93.75%
24	89.47%	31.25%	1.45	42.11%	97.92%
25.5	84.21%	33.33%	1.55	36.84%	97.92%
26.5	84.21%	35.42%	2.1	31.58%	97.92%
28	84.21%	39.58%	2.7	26.32%	97.92%
29.5	78.95%	45.83%			
30.5	73.68%	47.92%			
31.5	73.68%	54.17%	**Cystatrin-C**		
33	63.16%	58.33%	**Alb (Yes) if ≥**	**Sensitivity**	**Specificity**
34.5	63.16%	64.58%	-1	100.00%	0.00%
35.5	57.89%	66.67%	0.25	100.00%	2.08%
36.5	57.89%	68.75%	0.55	100.00%	4.17%
39	57.89%	70.83%	0.65	100.00%	12.50%
41.5	57.89%	75.00%	0.75	100.00%	20.83%
42.5	57.89%	77.08%	0.85	100.00%	50.00%
44	57.89%	79.17%	0.95	94.74%	60.42%
46	52.63	81.25%	1.05	94.74%	66.67%
47.5	42.11%	83.33%	1.15	94.74%	79.17%
49	42.11%	85.42%	1.25	78.95%	83.33%
50.5	42.11%	89.58%	1.35	78.95%	91.67%
51.5	36.84%	89.58%	1.45	68.42%	91.67%
54	36.84%	90.54%	1.55	63.16%	91.67%
62	31.58%	91.67%	1.7	57.89%	93.75%
72.5	31.58%	93.75%	18.5	36.84%	93.75%
79.5	31.58%	95.83%	1.95	26.32%	93.75%

Fig 1: ROC Curve



Area under curve

Test Result Variable(s)	Area	Std. Error(a)	Asymptotic Sig (b)	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
Blood Urea	.704	.077	.010	.553	.855
Creatinine	.776	.071	.000	.636	.916
Cystatin C	.908	.037	.000	.836	.980

The test result variable(s): Blood Urea, Creatinine, Cystatin C has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased. a. Under the nonparametric assumptions; b. Null hypothesis :true area =0.5

DISCUSSION

The body muscle mass and dietary factors have an influence on the production of Creatinine. Creatinine is filtered by the glomeruli, and also secreted by the renal tubules. This tubular secretion contributes approximately 20% of the total creatinine excretion by the kidney and it can increase as GFR decreases. All of these factors explain why serum creatinine concentration may not be a good parameter for accurate determination of GFR, especially at lower rates[6].On the other hand Cystatin C production in the body is a stable process that is not influenced by renal conditions, increased protein catabolism, or dietetic factors. Further, it does not change with age or muscle mass like creatinine does. Its biochemical characteristics allow free filtration in the renal glomerulus, and subsequent metabolism and reabsorption by the proximal tubule. For these reasons, serum cystatin C has been suggested to be an ideal endogenous marker of GFR.[7-9] However, few studies demonstrate that older age is independently associated with higher serum cystatin C levels after adjusting for creatinine clearance.[10]

Recently, several studies have suggested that cystatin C levels may be a more sensitive marker of early renal impairment than either albuminuria or serum creatinine concentration.[11-14] Cystatin C is a novel measure of kidney function that seems to overcome the limitations of serum creatinine concentration. Cystatin C is a cysteine protease inhibitor that is produced by virtually all nucleated cells and released into the bloodstream. It is entirely filtered by the kidney glomerulus and metabolized by the proximal tubule. [15] Many studies have shown that cystatin C may be a more sensitive indicator of mild renal impairment and may better estimate the GFR than serum creatinine.[16]

CONCLUSION AND RECOMMENDATIONS

Cystatin C appears to be a better marker for detection of diabetic nephropathy in comparison to blood urea and serum creatinine. Slight derangement in levels appeared more significant. We do not know whether it is a good early marker for detection. Its role should be ascertained through prospective control studies in normo albuminuric patients till they develop micoalbuminuria. Whether dyslipidaemia and nephropathy go hand in hand needs further evaluation so as to determine role for monitoring both parameters

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