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To Study the Effect of ACE Inhibitors on Serum Cystatin C in Early Diabetic Nephropathy Patients

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Abstract
Aims & Objectives: To study the effect of ACE inhibitors on serum Cystatin C in early Diabetic Nephropathy patients.
Materials & Methods: An interventional, analytical study being conducted in the department of Pharmacology & Medicine of HIMS, Dehradun over a period of 12 months. 36 Patients fulfilling the inclusion criteria were recruited in the study & specific baseline investigations like Serum Cystatin C, HbA1c & urinary albumin were done. Drug Ramipril 2.5-5 mg was prescribed once daily for a period of 3 months after which repeat investigations were done.
Results: The average Pre and Post-therapy Serum Cystatin C levels were 0.95 mg/l and 0.73 mg/l, HbA1C was found to be 9.92% and 9.06% and urinary albumin levels were 154.37 mg/l and 145.99 mg/l respectively.
Conclusion: Post Ramipril therapy, urinary albumin and Serum Cystatin C significantly declined suggestive of improved renal function in early diabetic nephropathy.

Keywords: Diabetic Nephropathy, ACE Is, Serum Cystatin C, Urinary Albumin

Introduction

Background

Diabetes is a disease of complications. DN is one of the major complication of DM, with high morbidity and mortality as well as major cause of end stage renal disease (ESRD). Early detection of DN and intervention in pre-clinical state can slow down disease progression thereby improving overall survival in patients with DN. The diagnosis of DN and its progression is routinely based on tests like albumin creatinine ratio, urinary albumin [1], GFR and kidney function tests, but as such none of these tests are specific or sensitive indicators for the diagnosis and progression of DN.

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 for early diagnosis and treatment. A Bio marker called Serum Cystatin C (Sr Cys C) has been shown to give most accurate results for diagnosis, prevention, progression and early detection of renal injury in type 2 diabetic patients [2].

There is high-level evidence that it's diagnostic sensitivity for the detection of even mildly impaired GFR, i.e; < 70 ml/min is far superior than the routine biomarkers used [3]. Its independence from height, gender, age, and muscle mass is an added advantage. By virtue of the fact that Sr Cys C diagnoses renal injury at a much earlier stage than any of the tests done routinely, it can have remarkably favourable impact on disease progression, patient survival and overall improved quality of life of the patient.

Interventions effective in slowing progression from microalbuminuria (MAU) to overt nephropathy include: (a) Strict glycemic control (b) Strict blood pressure control (c) Management of dyslipidemia and (d) Early intervention by drugs like ACEIs and ARBs [4].

Owing to the fact that there is lack of specific diagnostic biomarkers for early detection and timely initiation of therapy, this study was planned to study the effect of ACE is on serum Cystatin C in early DN patients.

Materials and Methods

This interventional,analytical study was undertaken in Himalayan Institute of Medical Sciences,Dehradun for a period of twelve months. Patients presenting to the Medicine OPD and primarily diagnosed with type 2 DM and fulfilling the inclusion criteria were recruited in the study, after obtaining written informed consent.

What this study adds

1) Early detection of DN by specific & sensitive biomarker Serum Cystatin C.
2) Slowing the progression of DN by early intervention by ACEIs.

Selection of the Subjects

The patients were recruited on the basis of the following criteria:

Inclusion criteria

1) Patients with type 2 DM of duration > 5 yrs.
2) Patients on oral hypoglycemic drugs (for at least 5 yrs).
3) Stage 1 hypertensives (as per JNC7 criteria).
4) Urinary albumin of < 300 mg/L
5) Glycosylated Hemoglobin ≥ 7 %
6) Cystatin C levels at baseline < 1.09 mg/L

Exclusion criteria

1) Diabetes Mellitus type 1
2) On insulin therapy
3) Stage II hypertensives (as per JNC 7 criteria).
4) Any cardiovascular complications
5) Urinary albumin > 300 mg/L
6) ESRD
7) Any other co morbid conditions.

Study Protocol

The demographic profile and detailed history was obtained from each patient, which included personal and family history, history of diabetes in family, duration of diabetes and treatment history. A general physical examination was performed and BP, weight, height, waist and hip measurement, Body Mass Index was determined in all the patients and the findings were entered in a pre-designed case recording form.

Blood samples for baseline estimation of serum cystatin C[5] and HbA1c were drawn by experts in phlebotomy section under direct supervision. Urine was sent for urinary albumin estimation to the reference laboratory.

After the baseline results were obtained the patients were enrolled in the study in accordance with the inclusion criteria. They were administered Ramipril 2.5-5 mg OD. The patients were periodically followed up every month for adherence to drug therapy and for any adverse drug reaction for a period of 3 months. At the end of three months repeat specific investigations - Sr Cys C, HbA1c and MAU were done. They were also enquired for presence of any adverse event due to the prescribed drug.

The treatment group was analysed by Microsoft excel 2010 and SPSS 19. The demographic profile of the study population like age, weight, height and BMI were expressed as mean ± standard deviation. The pre & post therapy comparison in the study group was done by paired't' test. Descriptive analysis was represented by graphical representation, percentage, pie chart using Microsoft excel 2010.

Results

Out of the total 36 patients in group as shown in Table 1. There were 26 male and 10 female patients (72.22% male and 27.77% female). The mean age of patients in group 50.97±9.53 years and the mean WHR was 1.00±0.089. The patients had mean weight of 72.91±12.91 Kg. The BMI was found to be 28.46±4.77 Kg/m^2 signifying that majority of the patients were overweight. This clearly denotes that weight is a major risk factor for increased prevalence of type 2 DM.

Table 2 shows the Investigational details of the patients in study Group that consisted of 36 patients. The mean MAU at baseline and post therapy was 154.37±74.27 & 145.99±72.72 mg/l respectively. Post therapy a decrease in MAU by 8.38 mg/l was recorded, which was found to be significant with a P value of <0.01. Similarly, values of Serum Cystatin C at baseline and post therapy were 0.95±0.29 & 0.73±0.23 mg/l respectively, which was significantly reduced by 0.213 mg/l with a P value of <0.01.

All the patients were enquired for any adverse reaction occurring due to study drugs throughout the study period of three months. Overall, adverse effects were observed in 2 patients in the study group. The predominant side effect was dry cough.

Discussion

DN is a progressively deteriorating kidney disease caused by damage to the capillaries in the glomeruli [6]. Early DN often has no symptoms. Clinical symptoms appear 5 to 10 years after significant kidney damage begins [7]. A decline in renal function, is assessed by MAU and Serum Cystatin C levels, of which Serum Cystatin C is regarded to be as a highly sensitive and specific marker for DN. It is now clear that the blockade of the RAAS not only reduces the BP but also slows the progression of renal disease in patients with DN [8]. RAAS has been targeted at different sites by various class of drugs. ACEIs reduces the production of Ang II by inhibiting the conversion of Ang I to Ang II by Angiotensin converting enzyme [9].

The preclinical diagnosis of renal injury was assessed by MAU. Due to which timely intervention was done, thus benefitting the patient in delaying the progression of the disease. Because of timely intervention by ACEIs the MAU was significantly decreased to 145.99mg/l from 154.37mg/l. In the 70.5% of the patients, at baseline had elevated levels of serum cystatin C with a mean of 0.95mg/l. In 30.5% of these patients, it reverted back within normal range. This was because of firstly preclinical detection of renal injury and then early intervention by ACEIs. No serious side effects were associated in the study group. The adverse effects were mild and there was no significant difference in both groups [10]. Cough was seen in two of the patients which were discontinued on therapy.

To conclude, the drug significantly reduced the MAU and Sr Cys C levels in type 2 diabetics with DN. The adverse effect profile was not serious or life threatening [11]. This indicates the potential of early diagnosis and timely pharmacological intervention in DN patients thereby retarding the course of disease by decreasing the progression of the renal injury.

Table 1: Demographic Profile of Patients in Study group (n=36).
(All values are expressed in Mean ± SD)

Sr. No.	Parameters	Study Group n=36
1	Age (years)	50.97±9.53
2	Sex Distribution (M/F)	26/10
3	Height (m)	1.60±0.08
4	Weight (kg)	72.91±12.91
5	Body Mass Index (Kg/m^2)	28.46±4.77
6	Waist Hip Ratio	1.00±0.089
7	Duration of DM (years)	7.08±1.66
8	HbA1c (Baseline)	9.92±1.94
9	HbA1c (3months)	9.63±1.48

Table 2: Pre & Post Therapy BP, MAU & Serum Cystatin C in Study Group (n=36).
(All values are expressed in Mean ± SD)

Sr. No.	Parameters	At Baseline	Post Therapy (3 months)	Difference	p Value
1	Blood Pressure (mm Hg)	127.88±15.59	124.72±9.99	-3.16±5.6	0.019*
2	Microalbuminuria (mg/L)	154.37±74.27	145.99±72.72	-8.38±1.55	0.003*
3	Serum Cystatin C (mg/L)	0.95±0.29	0.73±0.23	-0.213±0.06	0.001*

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Limitations of the Study

1) Small sample size: The sample size could be increased so that the differences in response among the different racial groups could be evaluated.
2) Short follow up peiod: A long follow up period, to strengthen and reinforce the results of the study and also to observe the long term side effects of the drugs.
3) Glycemic control: The poor glycemic control throughout the study could have affected the results of specific tests.

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Conflicts Of Interest

The authors declare that they have no competing interests.

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Ethics Committee Approval

Institutional Ethics Committee, HIMS, SRHU, Dehradun

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