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Role Of Cystatin C And Beta2microglobulin In Establishing Early Renal Dysfunction In Type2 Dm

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I. INTRODUCTION

Diabetes mellitus refers to disorders that have a common abnormality of raised blood glucose levels. Diabetes is classified into type 1 (autoimmune beta-cell destruction and absolute insulin deficiency) and type 2 (relative insulin deficiency and resistance(1)

The patients of Type 2 Diabetes Mellitus have a long asymptomatic period of hyperglycemia before the diagnosis can be made, whereas patients of Type 1 Diabetes Mellitus present with a short duration of hyperglycemia(1).

Diabetes is associated with many complications, mainly microvascular complications likeRetinopathy, Neuropathy, Nephropathy, andMacrovascular complications like coronary artery disease, peripheral artery disease,cerebrovascular disease.

India is one of thecountries of the INTERNATIONAL DIABETES FEDERATION. A total of425 million people have diabetes globally, and 82 million people in the Southeast AsianRegion, and by 2045, this will rise to 151 million. There were over 72,946,400 cases of diabetes in India as of 2017. (2)

Diabetic Nephropathy is a public health concern leading to a significant reduction in the life expectancy of diabetic patients. (3) Without any sugar control intervention, 20-40% with Microalbuminuria (MA) progress to Nephropathy after 20 years from the onset of diabetes, and approximately 20% develop endstage renal disease(ESRD).(4) DiabeticNephropathyisa microvascular complicationandisthe leading cause of ESRD worldwide. (5)

One of the significant complications of diabetes is Nephropathy, which leadsto the progressive development of chronic renal failure and decrease in GFR. Glomerular filtration rate (GFR), a kidney function marker, ismeasured by injecting compounds like inulin,radioisotopes like ^{51}chromium-EDTA,^{125}I-iothalamate,^{99m}Tc- DTPAor radiocontrastagentssuchasiohexol,butthesetechniquesare complicated, costly, time-consuming withside effects.[6][7] Creatinine is the most commonly used marker of kidney function but is inaccurate in mild renal impairment, and levels vary with muscle mass but not with protein intake. Formulas like the Cockcroft and Gault formula andthe MDRD formulatrytoadjust for these variables. (6)

Diabetesmellitusisa"**Silent epidemic**"spreadinglikewildfirethroughoutthe developing world. India has been termed dubiously as the "Diabetes capital of the world," with the number of patients expected to cross 79.4 million by the year 2030. (6)

Diabetic Nephropathy refers to specific pathologic structural and functional changes seen in the kidneys of patients with type 1 or 2 diabetes characterized by proteinuria, hypertension, and progressive reduction in kidney function.

DiabeticNephropathyischaracterizedbythefollowing(7)

- Persistentalbuminuriaofvalues(>300mg/dor>200µg/min)thatisconfirmedbyatleasttwooccasionswithinthree-sixmonthsapart
- AProgressivedecreaseintheglomerularfiltrationrate(GFR)
- Elevatedarterialbloodpressure.

Generally, DN is considered after a routine urinalysis screening showing Microalbuminuria in long-standing Diabetes Mellitus patients. Studies have shown that early intervention slows the onset of diabetic kidney disease in both Type 1 and Type 2 Diabetes Mellitus. (8)

The need for this study is to predict the early detection of diabetic Nephropathy, thereby stratifying patients who are at increased risk for renal failure. The cystatin C is elevated in these patients even before there

is a rise in serum creatininelevels,and the Beta 2 Microglobulinisincreased in urine and decreased in the serum of the patients of Diabetic Nephropathy, thereby ensuing early detection for the development of renal failure.
AIM: Tostudycystatincandbeta2microglobulinlevelsinestablishingrenal dysfunction in type2 diabetes mellitus

OBJECTIVES:
1.Estimationof cystatin cand beta2microglobulin levels in Type2 Diabetes Mellitus.
2. To Correlate these values with non-albuminuria and albuminuric subjects of Type 2 diabetes mellitus.
3. TocorrelatetheselevelswithestimatedGFRcalculatedfrom aCockcroft- gault formula using serum creatinine.

II. MATERIALSANDMETHODS

STUDYDESIGN:Hospital-BasedProspectivestudy
STUDYSUBJECTS: Patients with TypeIIDiabeteswhoare fulfilledthe below-mentioned inclusionand exclusion criteria were included in the study.
STUDYSETTING: PatientsadmittedinMedicalwardsinSRIVENKATESWARARAMNARAINRUIA GOVERNMENT GENERAL HOSPITAL, TIRUPATI
STUDYPERIOD: OneyearfromthedateofEthicalCommitteeapproval.(16/2/2019TO15/2/2020)
STUDYSAMPLESIZE : Samplesizecalculatedas80withcorrelationcoefficient-0.31andpower90%.

INCLUSIONCRITERIA :
1. PatientswithT2DMwhoparticipatedinthestudywithavalidinformedwritten consent.

EXCLUSIONCRITERIA:

1. Patientsdiagnosedpreviouslywithanycancer,MI,stroke,peripheral arterial disease, thyroid disorders, UTI.
2. Patientswhowereinsepsisandcriticallyill.
3. Patientsonsteroidsoranydrugswhichcausesproteinuria.
4. PatientspreviouslydiagnosedwithNephropathyandCKD.

STUDYMETHODS

Detailed History and Physical examination and eGFR calculation was done in every patient as per structured performa. Routine Investigations –like FBS/PPBS, urine albumin level, urine 24-hour protein levels and serum creatinine, total serum protein and serum albumin, USG abdomen, thyroid profile were done. Special investigations like serumcystatin C and beta 2 microglobulin were also done further.

III. RESULTS AND ANALYSIS:

80 patients with T2DM who fulfilled inclusion and exclusion criteria are included in the present study. Results are analysed and discussed.

1.AGE DISTRIBUTION :

In the present study the maximum number of patients are in the age group of 60 to 70 years (31.2%).followed by in the age group of 40 to 50 years(19%).The least number of patients are in the age group of 30 to 40 years accounting for 8.7%.

TABLE 1. AGE DISTRIBUTION

S.No	AGE IN YEARS	NUMBER OF PATIENTS	PERCENTAGE
1	30 – 40	7	8.70%
2	40 – 50	19	23.70%
3	50 – 60	18	22.50%
4	60 – 70	25	31.20%
5	70 – 80	11	13.75%

2. SEX DISTRIBUTION:
In the present study , 83% of the study subjects are male. Male predominance is observed in the present study with a male to female ratio of 4.7:1 is seen.

TABLE 2.1:SEX WITH MEAN CYSTATIN C AND MEAN BETA 2 MICROGLOBULIN

S.NO	SEX	MEAN CYSTATIN C FOR SEX	MEAN BETA2 MICROGLOBULIN FOR SEX
1	MALE	0.88	1.83
2	FEMALE	0.78	1.95

In our study , the mean cystatin C for male patients are 0.88 mg/dl while the female patients are having a mean cystatin C as 0.78mg/dl.In this study the mean beta 2 microglobulin for male patients are 1.83 while the mean beta 2 microglobulin for the female patients are found to be 1.95

TABLE 2.2: ESTIMATION OF CYSTATINC AND BETA2 MICROGLOBULIN WITH GENDER:

	GENDER	N	Mean±SD	t value	p value
Cystatin C	Male	66	0.89±0.32	1.113	0.269
	Female	14	0.79±0.22		
B2M	Male	66	1.84±0.51	-0.789	0.433
	Female	14	1.95±0.44		

Stats tool: Independent t test

No significant difference in the cystatin c and B2M values between genders in the present study

3. DURATION OF DIABETES:

In the present study the maximum number of patients are having diabetes between 5 to 10 years (45%) followed by 1- 5Yrs(15%). 11.25% of study subjects are detected T2DM at the time of admission into the hospital. 6.25% of patients having more than 20 yrs duration .

TABLE 3.1: DURATION OF DIABETES:

S.NO.	DURATION IN YEARS	NUMBER OF PATIENTS	PERCENTAGE
1	DENOVO	9	11.25%
2	<1	4	5%
3	1 TO 5	12	15%
4	5 TO 10	36	45%
5	10 TO 15	6	7.50%
6	15 TO 20	8	10%
7	>20	5	6.25%

TABLE 3.2:DURATION WITH MEAN CYSTATIN C AND MEAN BETA2MICROGLOBULIN

S.NO	DURATION IN YEARS	MEAN CYSTATIN C FOR DURATION	MEAN BETA2 MICROGLOBULIN FOR DURATION
1	DENOVO	1.17	2.24
2	<1	0.66	1.47
3	1 TO 5	0.84	1.58
4	5 TO 10	0.87	1.87
5	10 TO 15	0.94	2.17
6	15 TO 20	0.69	1.74
7	>20	0.69	1.74

In our study , the mean cystatin C for newly detected patients are at a higher level of 1.17 mg/dl and the next highest mean values are noted in patients with 10 to 15 years of diabetes and the next highest mean values are noted in patients with 1 to 5 years of diabetes. The patients with 15 to 20 years and those above 20 years of diabetes are found to have no change in mean value.

In this study the mean beta 2 microglobulin is highest for denovo detected patients with a mean value of 2.24, while next highest are seen in patients with 10 to 15 years duration with value of 2.17. It is to be noted that there is no change in the mean beta 2 microglobulin levels for patients with duration of 15 to 20 years and those above 20 years as both are having a mean value of 1.74.

TABLE 3.3:ESTIMATION OF CYSTATIN C AND BETA 2 MICROGLOBULIN WITH DURATION OF DISEASE:

	DURATION	N	Mean	Std Dev (SD)	F value	p value
Cystatin C	DENOVO	9	1.1711	.46560	2.764	**0.018**
	<1	3	.6633	.28711		
	1 – 5	13	.8454	.24751		
	5 – 10	36	.8700	.28159		
	10 – 15	6	.9450	.27501		
	15 – 20	8	.6988	.19621		
	>20	5	.6900	.08456		

B2M	DENOVO	9	2.2489	.37062	2.678	**0.021**
	<1	3	1.4733	.76271		
	1 – 5	13	1.5869	.42919		
	5 – 10	36	1.8764	.51954		
	10 – 15	6	2.1750	.27537		
	15 – 20	8	1.7463	.42416		
	>20	5	1.7540	.36746		

Stats tool: One way ANOVA
Inference: Significant difference between groups

Bonferroni Post-hoc analysis done, significant pairs illustrated below:
Cystatin C denovo vs. 15 to 20 years – Mean difference =0.472 (p=0.026)
B2M denovo vs. 1 to 5 years– Mean difference = 0.662 (p=0.037)
There is a significant difference in duration of diabetes to the levels of cystatin c and B2M as p -values are 0.018 and 0.021 respectively.

4. TYPE 2 DIABETES WITH COMORBIDITIES:

In the present study about 43.75% of study subjects are only diabeties without any co morbidities. Co morbidities observed in the present study are Hypertension, Chronic liver diseases, COPD. Most common co morbidity observed is Hypertension seen in 47.5% of patients.

TABLE 4. TYPE 2 DIABETES WITH COMORBIDITIES:

S.NO	COMORBIDITIES	NUMBER OF PATIENTS	PERCENTAGE
1	ONLY DIABETES	35	43.75%
2	DIABETES WITH HYPERTENSION	38	47.50%
3	DIABETES WITH TUBERCULOSIS	3	3.75%
4	DIABETES& CHRONIC LIVER DISEASE	2	2.50%
5	DIABETES WITH COPD	2	2.5%

5. TREATMENT HISTORY :

In the present study about 61.25% of patients are taking anti diabetic medications (OHA) and about 26.25% are on treatment with only insulin whereas 11.25% of patients are not on any treatment detected during the time of admission , while rest 1.25% are taking both anti diabetic medications and insulin combined together in view of uncontrolled sugars.

TABLE 5. TREATMENT HISTORY

S.NO	TREATMENTS	NUMBER OF PATIENTS	PERCENTAGE
1	NO TREATMENT	9	11.25%
2	ORAL HYPOGLYCEMIC DRUGS(OHA)	49	61.25%
3	INSULIN	21	26.25%
4	BOTH OHA AND INSULIN	1	1.25%

6. DISTRIBUTION OF EGFR:

In the present study about 33.75% of patients are having EGFR in the range of 60 to 90ml/min/1.73m^2 and 32.5% are with EGFR 30 to 60 ml/min/1.73m^2 and remaining 17.5% with EGFR >90 ml/min/1.73m^2, and 13.75% with EGFR 15 to 30 ml/min/1.73m^2 . About 2.5% are having EGFR <15 ml/min/1.73m^2 are detected as type 2 diabetes mellitus at the time of admission.

TABLE 6.1 : DISTRIBUTION OF EGFR

S.NO	EGFR	NUMBER OF PATIENTS	PERCENTAGE
1	>90	14	17.50%
2	60 – 90	27	33.75%
3	30 – 60	26	32.50%
4	15 – 30	11	13.75%
5	<15	2	2.50%

EGFR WITH MEAN CYSTATIN C LEVELS :

In the present study the mean cystatin C is at a higher value in patients with EGFR >90 ml/min/1.73m^2 (0.99) followed by patient with EGFR of 30 to 60 ml/min/1.73m^2 (mean value of 0.88)

TABLE 6.2. EGFR WITH MEAN CYSTATIN C LEVELS:

S.NO	EGFR	NO. OF PATIENTS	MEAN CYSTATIN C
1	>90	14	0.99
2	60-90	27	0.82
3	30-60	26	0.88
4	15-30	11	0.78
5	<15	2	0.78

The present study shows 14 patients who have an egfr >90 ml/min/1.73m^2 about 11 patients (78.5%) are having cystatin C above the normal level. Among 27 patients who are having Egfr 60 to 90 ml/min/1.73m^2 about 12 patients (44.5%) are having serum cystatin c above 0.8mg/dl. In patients with Egfr with 30 to 60 ml/min/1.73m^2 out of 26 patients only 7 patients (27%) are having rise in serum cystatin C above normal limit. While in patients with Egfr 15 to 30 ml/min/1.73m^2 and <15 ml/min/1.73m^2 which included 11 and 2 patients respectively none are having a rise in serum cystatin C .

These results shows that EGFR is linearly proportion to the cystatin c levels.

TABLE:6.3: EGFR WITH BETA 2 MICROGLOBULIN LEVELS

S.NO	**EGFR**	**NO. OF PATIENTS**	**MEAN BETA 2 MICROGLOBULIN**
1	>90	14	2.07
2	60 -90	27	1.86
3	30-60	26	1.94
4	15-30	11	1.37
5	<15	2	1.79

In the present study the highest mean value of beta 2 microglobulin is seen in patients with EGFR of >90 with value of 2.07 followed by patients with EGFR with 30 to 60 with a mean value of 1.94. The patients with a EGFR of 60 to 90 are having EGFR of 1.86 while patients with EGFR of <15 are having a mean beta 2 microglobulin of 1.79 and the least mean value is noted in patients with EGFR of 15 to 30 with a value of 1.37.

TABLE :6.4: ESTIMATION OF MEAN CYSTATIN C AND B2M WITH EGFR :

	EGFR	N	Mean	Std Dev (SD)	F value	p value
Cystatin C	>90	14	.9993	.43913	1.028	0.399
	60 -90	27	.8237	.29757		
	30-60	26	.8877	.23207		
	15-30	11	.7882	.29127		
	<15	2	.7850	.27577		
B2M	>90	14	2.0721	.43201	3.931	**0.006**
	60-90	27	1.8607	.56143		
	30-60	26	1.9481	.38447		
	15-30	11	1.3773	.36868		
	<15	2	1.7900	.74953		

Stats tool: One way ANOVA

Inference: Significant difference between groups only for B2M

Bonferroni Post-hoc analysis done, significant pairs illustrated below:

- Group >90 ML vs. 15 -30 ML – Mean difference = -0.695 (p=0.004)
- Group 60-90 ML vs. 15 -30 ML – Mean difference = -0.483 (p=0.048)
- Group 30-60 ML vs. 15-30 ML – Mean difference = -0.570 (p=0.010)

A statistical significance is observed between the B2M levels and various groups of EGFR. Whereas no statistical difference is observed between cystatin c levels and various groups of EGFR**.**

Table :6.5: Correlation Of Cystatin C And Beta 2 Microglobulin Levels With Estimated Gfr Calculated From Cockcroft-Gault Formula Using Serum Creatinine

Stats tool: Pearson Correlation between cystatin C & B2M against EGFR

		EGFR
Cystatin C	Pearson Correlation Coefficient (r)	0.206

	Significance (p value)	0.066
B2M	Pearson Correlation Coefficient (r)	0.321
	Significance (p value)	**0.004**

Interpretation:

- No correlation exist between cystatin c and EGFR levels
- Significant minimal positive correlation exist between B2M and EGFR levels

7.DISTRIBUTION OF URINE ALBUMIN :

In the present study about 30% of patients are not having albuminuria at the time of admission while a 70% of patients are having albuminuria at the time of admission .

TABLE 7.1: DISTRIBUTION OF URINE ALBUMIN

S.NO	ALBUMINURIA	NUMBER OF PATIENTS	PERCENTAGE
1	**ABSENT**	**24**	**30%**
2	**PRESENT**	**56**	**70%**

TABLE 7.2: DISTRIBUTION RANGE OF ALBUMINURIA IN PATIENTS

S.NO	ALBUMINURIA	NUMBER OF PATIENTS (56)	PERCENTAGE
2	TRACE	8	14.28%
3	1+	22	39.28%
4	2+	21	37.5%
5	3+	4	7.14%
6	4+	1	1.78%

TABLE: 7.3:. ALBUMINURIA WITH MEAN CYSTATIN C :

S.NO	ALBUMINURIA	NO. OF PATIENTS	MEAN CYSTATIN C
1	PRESENT	56	0.89
2	ABSENT	24	0.80

In the present study it is seen that the mean cystatin C is 0.89 for patients with albuminuria at the time of admission whereas patients with no albuminuria are having a mean cystatin C value of 0.80.

TABLE: 7.4: DISTRIBUTION OF CYSTATIN C WITH ALBUMINURIA

S.NO	ALBUMINURIA	NO. OF PATIENTS	MEAN CYSTATIN C
1	TRACE	8	1.18
2	1+	22	0.83
3	2+	21	0.86
4	3+	4	0.75
5	4+	1	1.37

In the present study it is seen that mean value of cystatin C is highest for patients with TRACE albuminuria. The patients with albuminuria of 1+ are having a mean value of 0.83 and the patients with 3+ albuminuria are having a mean cystatin C of 0.75.

TABLE: 7.5:ALBUMINURIA WITH MEAN BETA 2 MICROGLOBULIN :

S.No	Albuminuria	No. Of Patients	Mean Beta 2 Microglobulin
1	Present	56	1.82
2	Absent	24	1.94

In the present study the mean beta 2 microglobulin is found to be higher in patients without albuminuria with a value of 1.94 while the patients with albuminuria are having a mean beta 2 microglobulin value of 1.82.

TABLE 7. 6: DISTRIBUTION OF BETA 2 MICROGLOBULIN WITH ALBUMINURIA:

S.NO	ALBUMINURIA	NO. OF PATIENTS	MEAN BETA 2 MICROGLOBULIN
1	TRACE	8	2.22

2	1+	22	1.63
3	2+	21	1.86
4	3+	4	1.68
5	4+	1	2.44

In the present study themean beta 2 microglobulin level are seen highest in patients with trace albuminuria with a value of 2.22. The mean value of 1.86 is seen in patients with 2+ albuminuria followed by patients with 3+ albuminuria with a mean value of 1.68 .

TABLE 7.7:ESTIMATION WITH URINE ALBUMIN:

		N	Mean±SD	t value	p value
Cystatin C	Absent	24	0.80±0.24	-1.262	0.211
	Present	56	0.89±0.33		
B2M	Absent	24	1.94±0.39	0.964	0.338
	Present	56	1.82±0.54		

Stats tool: Independent t test

Inference:No significant difference in the cystatin c and B2M values between presence and absence of urine albumin

TABLE 7.8: TO CORRELATE THESE VALUES WITH NON-ALBUMINURIA AND ALBUMINURIC SUBJECTS OF TYPE 2 DIABETES MELLITUS:

Stats tool: Pearson Correlation between cystatin C and B2M

	Non-Albuminuric	Albuminuric
Pearson Correlation Coefficient (r)	0.068	0.605
Significance (p)	0.754	**<0.001**

Interpretation:No correlation exist between cystatin c and B2M levels in non albuminuric individuals .Significant moderate positive correlation exist between cystatin c and B2M levels in albuminuric individuals

8. Estimation of Cystatin C and B2M with Albuminuria:

There is a significant difference observed between lower levels of urine albumin to B2M with a p value of 0.013. There is no statistical significance between cystatin c and urine albumin levels.

Table:8.1 Estimation of Cystatin C and B2M with Albuminuria

	URINE ALBUMIN	N	Mean	Std Dev (SD)
Cystatin C	NIL	24	.8033	.23533
	TRACE	8	1.1875	.49497
	1+	22	.8323	.23847
	2+	21	.8605	.26513
	3+	4	.7550	.45829
	4+	1	1.3700	-.
B2M	NIL	24	1.9400	.39181
	TRACE	8	2.2288	.39091
	1+	22	1.6359	.46573
	2+	21	1.8614	.58076
	3+	4	1.6800	.55660
	4+	1	2.4400	-.

Stats tool: Kruskal Wallis test (As group 6 have n=1, one way ANOVA is not possible)

Inference: Significant difference between groups only for B2M (p=0.0.13)

Post Hoc Analysis:Significant difference was present between trace & 1+ Albuminuria (p=0.017)

9. ESTIMATION OF CYSTATIN C AND BETA 2 MICROGLOBULIN LEVELS IN TYPE 2 DIABETES MELLITUS.

The meancystatin c in the present study is 0.87±0.31with a range of 0.30 to 2.15. The meanB2M in the present study is 1.86±0.49 with a range of 0.00 to 2.66.

TABLE:9.1: ESTIMATION OF CYSTATIN C AND BETA 2 MICROGLOBULIN LEVELS IN TYPE 2 DIABETES MELLITUS.

Cystatin C	***B2M***
Total Patients (N): 80 Mean: 0.87±0.31 Range: 0.30 to 2.15	Total Patients (N): 80 Mean: 1.86±0.49 Range: 0.00 to 2.66

IV. DISSCUSSION:

This study is undertaken with the objective of Estimation of Cystatin c and Beta 2 microglobulin levels in Type 2 diabetes Mellitus and to correlate these values with non albuminuria and albuminuric subjects of Type 2 diabetes mellitus and also to correlate these levels with estimated GFR of these patients.

1.AGE AND SEX DISTRIBUTION:

In the present study the age ranges from 30 to 76 years . The maximum number of patients are in the age group of 60 to 70 years (31.2%).followed by in the age group of 40 to 50 years(19%).The least number of patients are in the age group of 30 to 40 years accounting for 8.7%. The mean age in the present study is 55.31 years . The similar observations are seen in the studies done by **S Avinash et al[9](**61.4 years)**, Durga Prasad Kedam et al[10] (**58.5 years), **Apakkan Aksun et al[11] (**59.9 years) .

2.SEX DISTRIBUTION :

In the present study , 83% of the study subjects are male(66 patients) and females accounted for 17%(14 patients). Male predominance is observed in the present study with a male to female ratio of 4.7:1. The male predominance is observed in the studies done by **Durga Prasad et al** where males contributing 66.1% of study subjects and **Varun Shetty et al[12]** where 65% are male subjects. But the male to female ratio is less when compared to the present study. Male to female ratio of more or less equal in the study done by **S Avinash et al (1.28: 1)** .

3. CORRELATION BETWEEN AGE AND SEX OF PATIENTS WITH SERUM CYSTATIN C AND BETA 2 MICROGLOBULIN LEVELS

In the present study the mean cystatin C for male patients is 0.88 mg/dl while the female patients are having a mean cystatin C of 0.78mg/dl. In this study the mean beta 2 microglobulin for male patients is 1.83 while the mean beta 2 microglobulin for the female patients are found to be 1.95.

There is no significant correlation has been found between the age and sex of the patients with the cystatin C and the beta 2 microglobulin levels in the present study .

Similarly **Avinash S et al** documented thatthere was no significance between age and sex of patients with the cystatin C levels in there study.**Aziza A Elsebai et al[13]** study also showed there is no statistical significance between beta 2 microglobulin levels and the age of the patients.

Apakkan Aksun et al study also showed that while serum creatinine differs among males and females the cystatin c and beta 2 microglobulin does not differ between sexes.

4. DURATION OF DIABETES:

In the present study the maximum number of patients are having diabetes between 5 to 10 years (45%) followed by 1- 5Yrs(15%). 11.25% of study subjects are detected T2DM at the time of admission into the hospital. 6.25% of patients having more than 20 yrs duration .

5. DURATION OF DIABETES WITH CYSTATIN C LEVELS :

In the present study , the mean cystatin C values are highest for denovo detected type 2 diabetes patients followed by patients with 10 to 15 years of diabetes . In the present study a significant positive correlation has been noted between duration of diabetes with the cystatin c levels (p value 0.018).

Durga Prasad Kedam et al also observed a significant difference between duration of diabetes and the cystatin C levels with p value (0.0001) in there study.

Varun shetty et al study has also found that there is a rise in cystatin C with the duration of diabetes.

6.DURATION OF DIABETES WITH BETA 2 MICROGLOBULIN LEVELS :

In the present study a significant positive correlation has been noted between duration of diabetes with the beta 2 microglobulin levels (p value 0.021).

Reem Abdelmohssin Ali et al[14]study also showed a positive correlation between the plasma beta 2 microglobulin levels and the duration of diabetes with a (p value 0.001).**Vaia D Raikou et al[15]**study showed that elevated rise in serum beta 2 microglobulin is especially noted in subjects with hyperglycemia and also in patients with inflammation irrespective of the presence of duration of diabetes mellitus.**Stephen P Juraschek et**

al [16]. study showed that serum beta 2 microglobulin were found to be increased in older age groups only in those subjects with a low EGFR value at the time of admission.

7. DIABETES WITH CO MORBIDITIES :

In the present study about 43.75% of study subjects are diabetics without any co morbidities. Co morbidities observed in the present study are Hypertension, Chronic liver diseases and COPD. Most common co morbidity observed is Hypertension seen in 47.5% of patients.

Magdalena Nowakowska et al[17]study also showed that among the patients with diabetes about 42.8% had hypertension as a most common co morbiditiy.. **Yukako tatsumi et al[18]** study showed that about 50% of diabetic patients had hypertension association significantly. **James R sowers et al[19]** found in there study that longer the duration of diabetes the more significantly the association with hypertension in these subjects.

Liang Li et al[20]study showed that among the diabetic patients around 8.5% of them had association with Tuberculosis after admission.In **Ashok kumar et al[21]** study group it was found that around 7 % of the diabetic study subjects were newly detected with pulmonary tuberculosis during hospital admissison.

8. EGFR WITH CYSTATIN C :

In the present study the mean cystatin C is at a higher value in subjects with EGFR >90 ml/min/1.73m^2 (0.99) followed by patient with EGFR of 30 to 60 ml/min/1.73m^2 (mean value of 0.88) . There is no significant correlation between the EGFR and Cystatin C levels in the present study (p value = 0.399).

. **Young Jae Jung et al[22]** study showed that even though cystatin C was a more sensitive indicator in patients with low GFR values (<60 ml/min/1.73m^2) than the serum creatinine, the GFR estimated using serum cystatin C levels was neither accurate nor specific hence it was advised that there is need for close monitoring of serum creatinine values in these patients

Masatomo Yashiro et al [23]study however showed that cystatin C rises in early renal dysfunction with a high sensitivity but many factors like inflammation, steroid therapy and also diabetes mellitus can cause cystatin C to elevate higher than the expected when compared to GFR using serum creatinine.

9. EGFR WITH BETA 2 MICROGLOBULIN :

In the present study the highest mean value of beta 2 microglobulin is seen in subjects with EGFR of >90 ml/min/1.73m^2 with value of 2.07 followed by subjects with Egfr with 30 to 60 ml/min/1.73m^2 with a mean value of 1.94. The subjects with a EGFR of 60 to 90 ml/min/1.73m^2 are having EGFR of 1.86 while subjects with EGFR of <15 ml/min/1.73m^{2}are having a mean beta 2 microglobulin of 1.79 and the least mean value is noted in patients with EGFR of 15 to 30 ml/min/1.73m^2 with a value of 1.37.

A statistical significance is observed between the B2M levels and various groups of EGFR in the present study..**Apakkan Aksun et al** showed that there was a rise a serum beta 2 microglobulin levels before a rise in serum creatinine levels, the study also showed a significant correlation between EGFR and the serum beta 2 microglobulin levels **(**p value- 0.001.)

Diego Real de Asúaet al[24] study also showed a significant correlation between egfr and beta 2 microglobulin levels even the kidney functions are only slightly disturbed.

Marco Colombo et al[25]study showed that beta 2 microglobulin can be used as a surrogate marker for decline in renal functions when compared to egfr and it was found to be significant with a p value of 0.0003. **Shahram Javadi et al[17]**also showed that there is a earlier rise in serum beta 2microglobulin levels before there is a rise in serum creatinine and blood urea nitrogen suggesting a potential role of serum beta 2 microglobulin as a bio marker in diabetes.

10.ALBUMINURIA WITH MEAN CYSTATIN C:

In the present study it has been found that the mean cystatin C is 0.89 for patients with albuminuria whereas the mean cystatin c is 0.80 for patients without albuminuria. Among the patients with albuminuria the mean cystatin C is highest for patients with 4+ albuminuria(1.37) followed by patients with TRACE albuminuria (1.18).

In the present study out of 24 patients who had no albuminuria about 14 patients (58.3%) have a rise in serum cystatin C levels indicating that the serum cystatin C levels rise in diabetic patients before albuminuria sets in.

There has been a statically significant difference observed between albuminuric and non albuminuric patients with the serum cystatin C levels (p value <0.001), however a statically significant difference cannot be established among the patients with different levels of albuminuria with the serum cystatin C levels. The similar observations were seen in the studies done by **Alaaeldin M. Bashier et al[26], Temesgen Fiseha et al[27], Mukherjee Brijesh et al[28], Durga Prasad Kedam et al and Yun Kyung Jeon et al[29].**

Alaaeldin M. Bashier et al study also showed that cystatin c can detect early onset diabetic nephropathy before microalbuminuria sets in which enables the timely intervention and further management. **Temesgen Fiseha et al** study also showed elevated levels of cystatin C levels in about 45.9% of normoalbuminuirc patients with type 2 diabetes mellitus, indicating that cystatin C can be used as a early biomarker for diabetic nephropathy before albuminuria .

Mukherjee Brijesh et al study showed that serum cystatin C can be a better marker for diabetic nephropathy than creatinine based EGFR but it is only equally as effective as albuminuria. The study demonstrated that patients with micro albuminuria with normal creatinine values had rise in serum cystatin C with showing statistical significance (p value<0.0001).

Yun Kyung Jeon et al study demonstrated that cystatin C was statistically significant between normoalbuminuria vs microalbuminuria (p value <0.05), microalbuminuria vs macroalbuminuria p value<0.001), normoalbuminuria vs macroalbuminuria p value<0.001)**Durga Prasad Kedam et al** study suggests that cystatin C levels are increased with renal tubular damage and can be used as a earlier marker before onset of albuminuria in diabetic patients.

11. ALBUMINURIA WITH BETA 2 MICROGLOBULIN LEVELS:

In the present study the mean beta 2 microglobulin is found to be higher in patients without albuminuria with a value of 1.94 than patients with albuminuria with a mean value of 1.82.

Among albuminuria patients themean beta 2 microglobulin level are seen highest in patients with trace albuminuria with a value of 2.22 followed by patient with 4+ albuminuria with a value of 2.44 and the least with patients of 1+ albuminuria with a mean value of 1.63.

Among patients with absent albuminuria (24 patients) about 16 patients (66.6%) have a rise in beta 2 microglobulin levels before albuminuria sets in indicating that it can used for early prediction for diabetic nephropathy.

A significant difference is observed between lower levels of urine albumin to Beta 2 microglobulin levels with a p value of 0.013.**Apakkan Aksun et al** showed statiscally significant difference in the serum beta 2 microglobulin levels and patients with normo/ micro/macro albuminuria with (p value0.0002).

V. CONCLUSION:

In the present study there is significant positive correlation is observed between Cystatin C and B2M levels when comparing albuminuric and non-albuminuric subjects. Among albuminuric subjects a significant correlation is observed only with Beta 2 microglobulin . A statistical significance is observed between the B2M levels and various groups of EGFR.

VI. LIMITATIONS:

Sample size is low .

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