



ASSOCIATION OF SERUM BETA 2 MICROGLOBULIN LEVELS IN CHRONIC KIDNEY DISEASE

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ABSTRACT **BACKGROUND:** Chronic kidney disease (CKD) is defined as a condition with renal damage or glomerular filtration rate $<60 \text{ ml/min/1.73m}^2$ for a period of 3 months. Over the last few decades many biomarkers have been devised in an attempt to diagnose chronic kidney disease earlier. There have been a lot of interest and research in this aspect. Certain biomarkers like cystatin C, NGAL, Kim 1, all have been studied extensively but none have come out as an independent marker in chronic kidney disease. Beta 2 microglobulin is a molecule present on MHC class I and present on almost all nucleated cells. Beta 2 microglobulin is a molecule which is secreted in the tubular system and reabsorbed also hence, can be used as a marker for both glomerular function and tubular function. Methods: Inpatients admitted with department of medicine and nephrology in MGM medical college and hospital were enrolled for the study as per inclusion and exclusion criteria. Prospective observational study was conducted. **Results:** showed a positive correlation between levels of beta 2 microglobulin and stages of chronic kidney disease. **Conclusion:** beta 2 microglobulin is a good and promising biomarker which can be used in the earlier diagnosis of chronic kidney disease.

KEYWORDS : beta 2 microglobulin, chronic kidney disease, observational study.

Introduction

Chronic kidney disease (CKD) is defined as a condition with renal damage or glomerular filtration rate $<60 \text{ ml/min/1.73m}^2$ for a period of 3 months¹.

Chronic kidney disease is a common public health issue in India and is associated with very high cardiovascular morbidity and mortality. According to a recent study it has been observed that in India the incidence of end stage renal disease is estimated to be 229 per million population and more than 1 lakh new patients undergo renal replacement therapy annually². Patients with renal failure on maintenance dialysis have excess mortality which is 8 times higher than that of the general population³.

Traditionally, glomerular filtration rate is considered to be an ideal marker of kidney function but glomerular filtration rate is time consuming and is usually therefore estimated from equations that make use of serum creatinine and cystatin C. Estimation of true glomerular filtration rate is very difficult so, an ideal substance that is freely filtered at the glomeruli and is neither reabsorbed nor secreted by renal tubules can be taken as an indirect marker for estimation of glomerular filtration rate⁴.

During the last century, serum creatinine has been the most widely used biomarker for diagnosing kidney disease. However owing to its limitations is only utilized in estimation of glomerular filtration rate by equations.

During the last decade, several novel biomarkers have emerged which allows the diagnoses of kidney diseases earlier. Although the specificity and sensitivity of such markers like kidney injury molecule 1 (Kim 1), neutrophil gelatinase associated lipocalin (NGAL), fibroblast growth factor 23, urine retinol binding protein 4 are high and shows promising results in the studies conducted thus far, none of them have been validated to make a clinical decision upon its positivity⁴.

Beta2-microglobulin (B2M) forms light chain of the Class I major histocompatibility complex (MHC). It is found on the surfaces of almost all nucleated cells. It is a non-glycosylated polypeptide with a molecular weight of 11.729kDa. Due to its small size, B2M is filtered by the glomerulus and is degenerated in the proximal tubules through a megalin-dependent pathway⁵.

In patients with a reduced glomerular filtration rate, circulating B2M levels are elevated. In dialysis patients, in whom the glomerular

filtration rate is almost completely abolished, B2M accumulates in the circulation far above its levels in normal subjects and is difficult to dialyze by use of low-flux membrane. There is data to demonstrate that plasma beta 2 microglobulin is a good endogenous marker of glomerular filtration rate and with decline in glomerular filtration rate there is increase of serum beta 2 microglobulin prior to serum creatinine. However due to lack of studies in the last decade on the use of beta 2 microglobulin in chronic kidney disease, this has limited its use in clinical practice⁴.

There are multiple biomarkers available for kidney injury other than creatinine like Cystatin C, Neutrophil Gelatinase Associated Lipocalin (NGAL), Kidney Injury Molecule-1 (KIM-1) and Beta 2 Microglobulin. Beta 2 Microglobulin has generated interest in the research off late. However, limited data is available for the same in Indian context. Hence, the present study was done with intent to fill this gap of relation between beta 2 Microglobulin and stages of CKD.

Aim and objectives

AIM

To study role of Beta 2 Microglobulin in chronic kidney disease.

Objectives

1. To study the levels of Beta 2 Microglobulin in chronic kidney disease.
2. To co-relate the levels of Beta 2 Microglobulin with different stages of chronic kidney disease. Material and Methods Present study is single center prospective, observational study.

Study Duration:

The study was conducted from December 2020 to November 2022

Source of patient:

Patients were recruited from out patient's department (OPD) and inpatient departments, under Department of General medicine and department of nephrology at tertiary care hospital.

Inclusion criteria:

Patient above the age of 18 years admitted as inpatients in the Department of Medicine and Nephrology diagnosed with chronic kidney disease based on KDIGO criteria which defines chronic kidney disease as: kidney damage or glomerular filtration rate (GFR) $<60 \text{ mL/min/1.73 m}^2$ for 3 months or more. Stages of CKD^{9,10}

- a. Stage 1: Kidney damage with normal or increased GFR ($>90 \text{ mL/min/1.73 m}^2$)

- b. Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m²)
- c. Stage 3a: Moderate reduction in GFR (45-59 mL/min/1.73 m²)
- d. Stage 3b: Moderate reduction in GFR (30-44 mL/min/1.73 m²)
- e. Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m²)
- f. Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m² or dialysis)

Exclusion criteria:

Any coexisting non-renal disease where beta 2 microglobulin can increase

1. Patients diagnosed with multiple myeloma
2. Patients diagnosed with lymphoma
3. Patients diagnosed with immunological conditions

Methodology :

Present prospective observational study was done at the Department of medicine and nephrology at a tertiary care hospital from duration of December 2020 to November 2022. 218 diagnosed chronic kidney disease patients were enrolled as per the inclusion criteria for the study. Institutes Ethical Committee approval was obtained prior to commencement of study. Patients fulfilling inclusion and exclusion criteria were enrolled. Informed written consent was obtained from all the participants and detailed procedure of the study was explained to each in their own language. Total 218 patient's clinical data were recorded on case record proforma (CRF) and detailed clinical examination was performed in each patient. Total patients were classified in different stages based on EGFR values and serum Beta-2 Micro globulins were recorded in all patients. Further these serum beta 2 microglobulin levels were co related with the glomerular filtration rate and stages of chronic kidney disease according to the EGFR calculation and results were obtained.

Statistical Analysis:

Data collected compiled in MS EXCEL Sheet 2018. Analysis of Data is done by SPSS Software Version 2.0. Qualitative data tabulated in the frequency and percentage form. Chi-square test has been used to test the proportions in association. Both Qualitative and Quantitative data represented in the form of visual impression like Bar Diagram, Pie Diagram. Microsoft word and Excel have been used to generate graphs, tables etc.

Chi-Square Test

$$\chi^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

E_i

Where O_i is observed frequency and E_i is Expected frequency

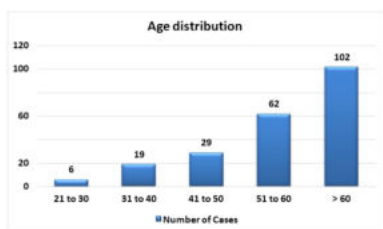
Observation and Results

A hospital based , single Centre, prospective study was conducted in 218 patients to analyze the role , levels and correlation of beta 2 microglobulin in chronic kidney disease. And the following result.

Table 1: Distribution of Cases according to Age

Sr. No.	Age group [Years]	Number of cases [N=218]	Percentage %
1	21 to 30	6	3 %
2	31 to 40	19	9 %
3	41 to 50	29	13 %
4	51 to 60	62	28 %
5	> 60	102	47 %
Total		218	100 %

Table 1 shows distribution of cases according to Age. Majority of cases i.e. 102 (47 %) were from age >60 years followed by 29 (13 %) cases from age group 41 to 50 years. Mean ± SD for age was 109.5 ± 63.07 (Graph 1)

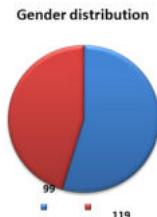


Graph 1: Distribution of Cases according to Age

Table 2: Distribution of Cases according to Gender

Sr. No.	Gender	Number of cases [N=218]	Percentage %
1	Male	119	54 %
2	Female	99	46 %
Total		218	100 %

Table 2 shows distribution of Cases according to Gender. Males were 119 (54 %) and females were 99 (46 %). Male to female ratio was 1.2: 1 (Graph 2)



Graph 2: Distribution of Cases according to Gender

Table 3: Distribution of Cases according to stages of Chronic Kidney Disease

Sr. No.	Stages of CKD eGFR (ml/min/1.73m ²)	Number of cases [N=218]	Percentage %
1	Stage 1 (> 90)	18	8 %
2	Stage 2 (60 to 89)	29	13 %
3	Stage 3a (45 to 59)	49	23 %
4	Stage 3b (30 to 44)	51	23 %
5	Stage 4 (15 to 29)	39	18 %
6	Stage 5 (< 15)	32	15 %
Total		218	100 %

Table 3 shows distribution of Cases according to stages of CKD. Stage 1 cases were 18 (8 %), stage 2 were 29 (13 %), stage 3a were 49 (23 %), stage 3b were 51 (23 %), stage 4 were 39 (18 %) and stage 5 were 32 (15 %) (Graph 3)

Graph 3: Distribution of Cases according to stages of Chronic Kidney Disease.

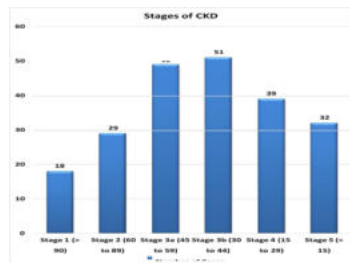
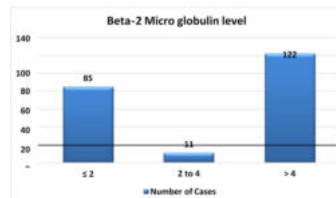


Table 4: Mean Beta 2 Microglobulin levels in different stages of Chronic Kidney Disease.

Sr. No.	Beta-2 Micro globulin (mg/L)	Number of cases [N=218]	Percentage %
1	≤ 2	85	39 %
2	2 to 4	11	5 %
3	> 4	122	56 %
Total		218	100 %

Table 4 shows distribution of Cases according to Beta-2 Micro globulin level. Beta-2 Micro globulin level ≤ 2 mg/L was found in 85 (39 %) cases, 2 to 4 mg/L was found in 11 (5 %) cases and > 4 mg/L was found in 122 (56 %) cases. (Graph 4)



Graph 4: Distribution of Cases according to Beta-2 Micro globulin level

Table 5: Mean Beta 2 Microglobulin Levels in different stages of Chronic Kidney Disease.

Sr. No.	Stages of CKD eGFR (ml/min/1.73m ²)	Beta-2 Micro globulin Mean ± SD	Total N (%)
1	Stage 1 (> 90)	2.12±1.44	18 (8 %)
2	Stage 2 (60 to 89)	1.99±0.92	29 (13 %)
3	Stage 3 (30 to 59)	3.69±1.99	100 (46 %)
5	Stage 4 (15 to 29)	5.25±0.98	39 (18 %)
6	Stage 5 (< 15)	5.24±1.29	32 (15 %)

Table 5 shows distribution of Cases according to Beta-2 Micro globulin level. Mean ± SD of stage 1 was 2.12±1.44, stage 2 was 1.99±0.92, stage 3 was 3.69±1.99, stage 4 was 5.25±0.98 and stage 5 was 5.24±1.29 (Graph 5)

Graph 5: Mean Beta 2 Microglobulin Levels in different levels CKD.

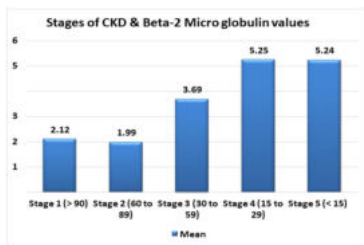


Table No 6: Co-relation of Beta 2 Microglobulin with different stages of Chronic Kidney Disease.

Sr. No.	Stages of CKD eGFR (ml/min/1.73 m ²)	Beta-2 globulin		Total N (%)	P value
		> 2 mg/L N (%)	> 4 mg/L N (%)		
1	Stage 1 (> 90)	0 (0 %)	2 (1 %)	2 (1 %)	< 0.00001 (S)
2	Stage 2 (60 to 89)	8 (4 %)	0 (0 %)	8 (4 %)	
3	Stage 3a (45 to 59)	3 (1 %)	22 (10 %)	25 (11 %)	
4	Stage 3b (30 to 44)	0 (0 %)	32 (15 %)	32 (15 %)	
5	Stage 4 (15 to 29)	0 (0 %)	37 (17 %)	37 (17 %)	
6	Stage 5 (< 15)	0 (0 %)	29 (13 %)	29 (13 %)	
Total	11 (5 %)	122 (56 %)	133 (61 %)		

Table 6 shows correlation of Cases according to CKD stages and Beta-2 Micro globulin level. Amongst 18 (8 %) stage 1 CKD cases 2 (1 %) were having >4 mg/L

Beta-2 Micro globulin. Amongst 29 (13 %) stage 2 CKD cases 8 (3 %) were having > 2 mg/L Beta-2 Micro globulin. Amongst 100 (46 %) stage 3 CKD cases 22 (10 %) were having > 4 mg/L Beta-2 Micro globulin and 3 (1 %) were having > 2 mg/L. Amongst 39 (18 %) stage 4 CKD cases 37 (17 %) were having > 4 mg/L Beta-2

Micro globulin. Amongst 32 (15 %) stage 5 CKD cases 29 (13 %) were having > 4 mg/L Beta-2 Micro globulin. Result obtained showed statistically significant correlation (P< 0.00001) interpreted as Stages of CKD affects Beta-2 Micro globulin values (Graph 6).

Results

Majority of the patients were from age >60 years, 102(47 %) patients were from age group >60 years, followed by 29(13 %) cases from age group of 41 to 50 years.

There was a male preponderance. Males were 119(54 %) while female patients were 99(46%) of study group.

Out of 218 patients enrolled stage 1 CKD had 18(8%) cases, stage 2

had 29(13%) cases, stage 3a had 49(23%) cases stage 3b had 51 (23%) cases, stage 4 had 39 (18%) and stage 5 had 32 (15%) cases respectively.

Out of 218 patients enrolled, 122 (56 %) cases had beta 2 microglobulin >4mg/l, 85 (39%) cases had beta 2 microglobulin <2mg/l and 11 (5 %) cases had beta 2 microglobulin 2 to 4 mg/l.

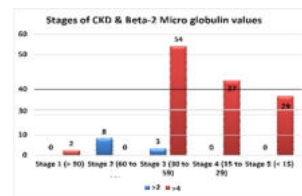
Serum beta 2 microglobulin levels were correlated with the stages of chronic kidney disease , the mean + standard deviation of each stage were as follows; stage 1 was 2.12 + 1.44, stage 2 was 1.99 + 0.92, stage 3 was 3.69 + 1.99, stage 4 was 5.25 + 0.98 and stage 5 was 5.24 + 1.29 . 122(56 %) cases out of 218 had beta 2 microglobulin levels >4mg/l. stage 1 had 2 (1%) cases of beta 2 microglobulin >4 mg/l, stage 2 had 0(0%) cases had beta 2 microglobulin >4 mg/l, stage 3a had 22 (10 %) cases had beta 2 microglobulin >4mg/l, stage 3b had 32 (15 %) cases had beta 2 microglobulin > 4 mg/l, stage 4 had 37 (17%) cases of beta 2 microglobulin > 4 mg/l and stage 5 had 29 (13 5) cases of beta 2 microglobulin > 4 mg/l with a p value <0.0001 showing stages of chronic kidney disease affects beta 2 microglobulin levels.

Conclusion

Beta 2 microglobulin has been studied as a marker for both glomerular function and tubular function, as after production in the body it is filtered by the glomerulus and most of it is reabsorbed by the proximal tubules. Thus, the levels correlate well with the damage that has occurred in the kidneys.

Study concluded a positive relationship amongst levels of beta 2 microglobulin and Chronic Kidney Disease.

Graph 6: Co-relation of Beta 2 Microglobulin with different stages of Chronic Kidney Disease.



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