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Urology

Co-Relation between Plasma Beta2 Microglobulin Level and Cardiac Performance Factors in CKD Patients

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Abstract **Original Research Article**

***Background*:** Cardiovascular disease mortality and morbidity is astonishingly high in CKD population. As renal function decreases beta2 microglobulin level starts to rise. There is an inverse relationship between e GFR and beta2 microglobulin level, but it is not established whether this protein causes cardiovascular dysfunction or not. This study was done to evaluate the relationship between plasma beta2 microglobulin level and cardiac performance in CKD patients. ***Objectives*:** To assess the beta2 microglobulin level in CKD and normal patients and to compare between them. To evaluate the relationship between beta2 microglobulin level and cardiac performance factors in CKD patients and to establish the relationship of beta2 microglobulin with eGFR. ***Materials and Methods*:** This case control study was done in DMCH from April 2017 to June 2018.86 patients were taken. Among them 46 patients were in case group and 40 patients were in control group. Case and control groups were labelled as group-I and group- II accordingly. Cases were taken from Nephrology outdoor and indoor unit of DMCH and also from cardiology outdoor unit. After selection of the patients informed consent was taken and blood send for beta2 microglobulin measurement in BSMMU, and Echo was done in DMCH cardiology department. For data analysis SPSS-24 was used. P value <o.o5 was and confidence interval at 95% was taken as significant. ***Result*:** Significant positive co-relation was found in between beta2 microglobulin level and CKD stages, thus negative co –relation with eGFR. Also beta2 microglobulin in group –I was 5.15±1.33 and in group –II it was 1.5±0.38 µgm/ml which was statistically significant. The cardiac performance factors like LVMI was found high in group –I(91.55±26.93) gm/m2and in group-II it was significantly low(77.4±21.7)gm/m2. The EF in group I was 62.96±4.03%, and in group –II it was 64.9±3.2%, which was also statistically significant. The other parameters like LVEDd and LVM was found non-significant. ***Conclusion*:** High plasma beta2 microglobulin level is associated with impaired cardiac performance factors in CKD patients.

Keywords: Cardiovascular disease, macroglobulin, chronic kidney disease.

INTRODUCTION

Chronic kidney disease (CKD) is a common public health issue associated with astonishingly high cardiovascular (CV) morbidity and mortality and high costs. Patients with renal failure on maintenance dialysis have excess mortality, that is, eight times higher than that of the general population according to USRDS data 2015.This is also true for our CKD populations. Most patients die due to CV events related to both traditional and non-traditional risk factors and this is true for both predialysis and dialysis patients [1].

Beta-2 microglobulin was first discovered in 1964 in the urine of subjects with Wilson's disease or cadmium poisoning by Berggard I *et al*., on 1968 [2]. It is a 100-amino acid protein of relatively small molecular weight (11,800 Da, size 11 Å) and it is encoded by a gene in chromosome 15 in humans. The secondary structure of the molecule consists of two large beta sheets that are linked together by a single disulfide bond and it was stated by Becker J *et al*., (1985) and Iwata K *et al*., (2007) [3, 4].

In contrast to the immunoglobulins, β2M does not form dimers but rather associates with the major histocompatibility complex I (MHC-I)/human leukocyte antigen I (HLA-I) on the surface of all nucleated cells. The interaction between β2M with the alpha chain of the HLA-I is essential for antigen presentation. It is present on the surface of nearly all nucleated cells and thrombocytes.

It is normally filtered readily at the glomerulas and is catabolized by proximal tubular cells of the kidney. Impaired renal function and hyper production are both associated with increased serum level. A function of beta 2 microglobulin as a modulator of lymphocyte surface and as a potential regulator of the immune system is proposed. (Berniere GM, 1980) Elevated beta2 microglobulin level can be observed in a range of hematological, immunodeficiency, autoimmune and renal diseases [5]. It is the most widely studied middle molecular weight protein in ESRD [6]. It is known to cause dialysis related amyloidosis, by virtue of its retention when renal function fails, its deposition in tissues, its aggregation into fibrils, and its ability to become glycosylated [7]. This protein has an active role in vascular damage by upregulation of IL-1 and TNF-α expression [8]. It might cause cardiovascular disease by amyloid formation [9]. This protein has an active role in vascular damage by upregulation of IL-1 and TNF-α expression [8].

Objective

General Objectives: To assess the association between serum β2 microglobulin level and cardiac status.

Specific Objectives

- To measure β2 microglobulin level in CKD group and control group and to correlate with eGFR.
- To evaluate the relationship between β2 microglobulin level with LVMI and also EF, LVEDd in CKD patients.
- To compare β2 microglobulin level between the normal population and CKD patients.

METHODOLOGY

Study Design: Cross sectional, observational study

Place of Study: Dhaka Medical College Hospital, Dhaka.

Study Period: April 2017-June 2018

Sources of Cases: Cases were taken from nephrology outpatient and inpatient department. When they fulfilled the inclusion criteria they were send for echocardiography in DMCH cardiology dept and blood send in BSMMU pathology dept for doing beta2 microglobulin test.

Controls were taken from doctors, sisters, office staffs and also from patients attendants.

Method of estimating sample size and the detailed sampling technique:

Sample size was calculated using the following formula:

$$n = \frac{(Z_\alpha + Z_\beta)^2 \times (\sigma_1^{\,2} + \sigma_2^{\,2})}{(\mu_1 - \mu_2)^2}$$

Here,

n= sample size

μ_1 = 36.8 [Mean B_2M in survivor group (Kim *et al*., 2011)]

μ_2 = 32.6 [Mean B_2M in non-survivor group (Kim *et al*., 2011)]

σ_1 = 12.3 [SD of B_2M in survivor group (Kim *et al*., 2011)]

σ_2 = 13.2 [SD of B_2M in non-survivor group (Kim *et al*., 2011)]

Z_α = 1.96 at a 95% confidence interval

Z_β = 0.85 at an 80% power

Putting the values in the above equation the sample size n is estimates as:

$$n = \frac{(1.96 + 0.85)^2 \times (12.3^2 + 13.2^2)}{(36.8 - 32.6)^2} = 146$$

So, Final sample size will be 146 in each group.
Study group = 146
Control group = 146

Sampling technique: purposive sampling

Selection criteria:

CASE

Inclusion Criteria:

Patients having CKD of different stages except on maintenance HD patients.

Exclusion Criteria:

- Patients with stage 5 CKD on MHD.
- Patients with known heart disease'
- Plasma cell dyscracia like Multiple Myeloma, Waldenstorm macroglobulinemia.
- Kidney transplantation.

Control:

Inclusion Criteria:

Normal healthy individuals who has no history of CKD, heart disease age group between.

Methods of data processing and statistical analysis: Unpaired t test was used for comparing the echocardiographic measures, pearson correlation test was used for detecting correlation between beta2 microglobulin level and LVMI, LVEDd, EF. Multivariate regression analysis was done to see the ralationshipof different variables on beta2 microglobulin

and anaemia and HTN. Demographic data was shown as mean+/-SD.

Computer program used for data analysis: SPSS 24 was used**.**

Statistical significance level set: p value<.05 was considered significant.

RESULTS

Table 1: Distribution of the study patients by demographic charecteristics (n=86):

Demographic Data (age & sex)	Group-I (n=46)		Group-II (n=40)	
	n	%	n	%
Age (in years)				
<50	**17**	**37.0**	**10**	**25**
50-60	**19**	**41.3**	**25**	**62.5**
>60	**10**	**21.7**	**05**	**12.5**
Mean±SD	**51.76±12.06**		**50.6±4.82**	
Max,Min	**15**	**,72**	**36**	**,64**
Sex				
Male	**33**	**71.7**	**30**	**75**
Female	**13**	**28.3**	**10**	**25**

Table 1 shows the demographic data (age & sex) of the study patients, it was observed that almost half (41.3%) patients belonged to age 50-60 years in group I and 25 (62.5.%) in group II. The mean age was 51.76±12.06 years with ranged from 15 to 72 years in group I and 50.6±4.82 years with ranged form 29 to 47 years in group II. Three fourth (71.7%) patients were male in group I and 30(75%) patients in group II.

Group-I=Case group

Group-II=Control group

Table 2: Distribution of the case group by disease status (n=46)

Disease status	Number of patients	Percentage
CKD stage		
1-3	**24**	**52.2**
4-5	**22**	**47.8**

Table 2 Interpretation: shows the distribution of the study patients by disease status. It was observed that more than half (52.2%) patients belonged to CKD stage 1-3. Majority (87.0%) had HTN. Most of patients (82.6%) had anemia.

Table 3: Comparison of the study patients by Beta 2 microglobulin (n=86)

	Group I (n=46)		Group II (n=40)		P value
	Mean±SD		Mean±SD		
Beta 2 microglobulin	5.15±1.33		1.5±0.38		0.001[s]
Range (min, max)	2.8	,10.24	0.8	,2.1	

s= significant

p value reached from unpaired t-test

Table 3 Interpretation: The mean beta 2 microglobulin was 5.15±1.33 with ranged form 2.8 to 10.24 in Group I and 1.5±0.38 with ranged form 0.8 to 2.1 in Group II. The difference was statistically significant (p<0.05) between two groups.

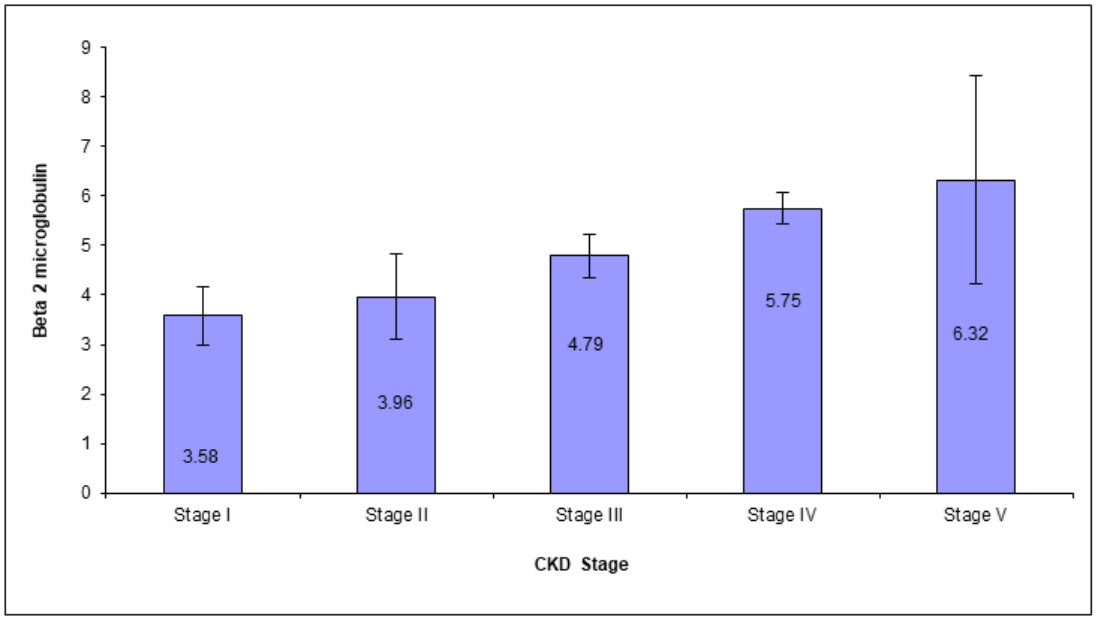

Figure 1: Bar diagrammatic representation of CKD stage and Beta2 microglobulin level

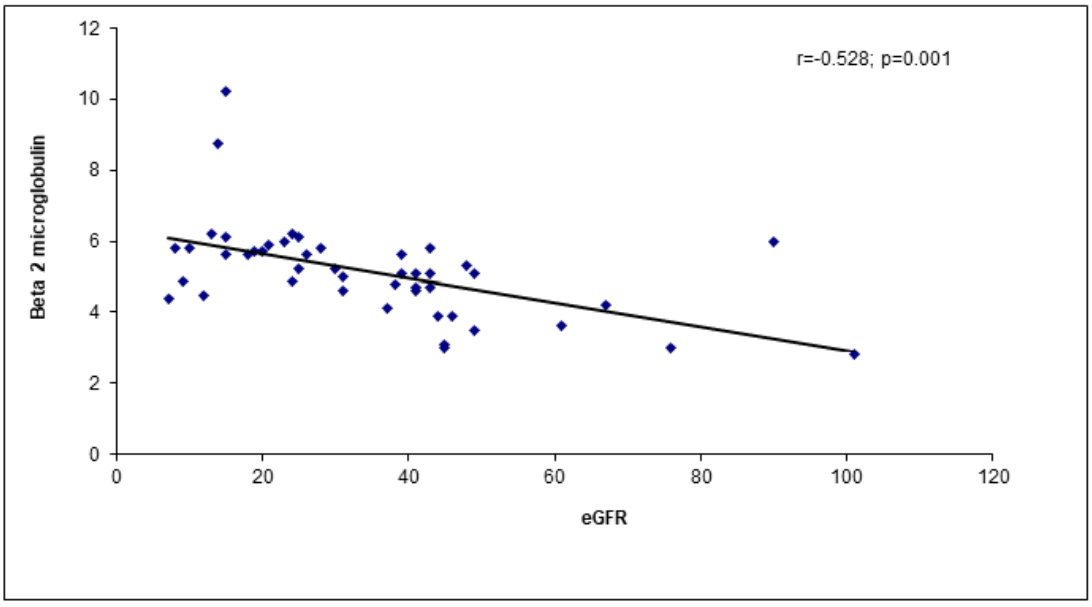

Figure 2: Scatter diagram showing negative significant correlation (r=-0.528; p=0.001) between eGFR and Beta 2 microglobulin

Table 4: Comparison of the study patients by cardiac function parameters (n=86)

Cardiac function parameters	Group-I (n=46)		Group-II (n=40)		P value
	Mean±SD		Mean±SD		
LVMI	91.55	±26.93	77.4	±21.71	0.043[s]
Range (min, max)	56	,180	56	,126	
LVED d	47.2	±7.46	47.9	±3.81	0.693[ns]
Range (min, max)	12	,59	42	,55	
LVM	143.33	±39.97	134.15	±25.65	0.352[ns]
Range (min, max)	88	,245	93	,181	
EF	62.96	±4.03	64.9±	3.2	0.017[s]
Range (min, max)	56	,72	58,	68	

s= significant, ns= not significant, p value reached from unpaired t-test

Table 4 Interpretation: The mean LVMI was 91.55±26.93 with ranged form 56 to 180 in Group I and 77.4±21.71 with ranged form 56 to 126 in Group II. The mean LVED d was 47.2±7.46 with ranged form 12 to 59 in Group I and 47.9±3.81 with ranged form 42 to 55 in Group II. The mean LVM was 143.33±39.97 with ranged form 88 to 245 in Group I and 134.15±25.65 with ranged form 93 to 181 in Group II. The mean EF was 62.96±4.03 with ranged form 56 to 72 in Group I and 64.9±3.2 with ranged form 58 to 68 in Group II. The difference LVMI and EF were statistically significant ($p<0.05$) between two groups.

DISCUSSION

This case control observational study was done in department of Nephrology in Dhaka Medical College Hospital during the period of April 2017-June 2018 to evaluate the level of beta2 microglobulin at different stages of CKD, and also in normal population. It also put on light over the relationship of beta2 microglobulin with decreased eGFR. Total 86 patients were taken. They were divided into two groups, as group-I and group –II. The group I patients were CKD populations of different stages and the group II were normal population. There were 46 cases and 40 controls in this study (due to time constraint). The CKD group of patients were taking conservative treatments only.

It is well established that there is an undeniable link between cardiovascular risk and kidney dysfunction and even in the stage of subtle kidney dysfunction, intensive prevention for the cardiovascular risk should be taken[10]. The uremic milieu and the uremic toxins both play a role for the development of cardiovascular disease, this study searches the role of beta2 microglobulin with cardiovascular disease.

The CKD populations were distributed according to disease status. The CKD stage 1,2,3 group consisted of 24 patients that is 52.2% and the CKD stage 4,5 group consist of 22 patients, that is 47.8%. Among the CKD group 87% was hypertensive and 82.6% patient was anaemic.

The demographic chart of this study shows that the mean age of group –I(CKD group) patients was 51.76±12.06 years and in case of group-II(control group) the mean age was 50.6±4.82 years, in group –I there was 33 male and 13 female, and in group –II there was 30 male and 10 females.

The mean beta2 microglobulin level in group –I patients was 5.15±1.33 µgm/dl,and in group-II it is 1.5±0.38 µgm/dl, and it was statistically significant. It confirms that decreased renal function is associated with increased beta2 microglobulin retention in CKD group of patients.

Residual kidney function is known to be an important determinant of serum beta2 microglobulin level, because the kidneys are the primary routes for the elimination of this protein [11]. This study is also in line with their statement as it shows that there is gradual increase in beta2 microglobulin level with the progression of CKD stages.

The figure 2 shows the association between beta2 microglobulin level and CKD stages thus there is a negative correlation between beta2 microglobulin level and eGFR. Stage I CKD patients have a mean beta2 microglobulin of 3.58±0.59 µgm/ml, stage II group has 3.96±0.86 µgm/ml, stage III has 4.79±0.44 µgm/ml, stage IV group has 5.7±0.31 µgm/ml, and stage V group has the highest level of beta2 microglobulin that is 6.32±2.1 µgm/ml. Liabeuf S *et al*., (2012), showed that beta2 microglobulin was progressively increased with CKD stage progression [12].

This study measured the cardiac function parameters between two groups, the mean LVMI of group-I patients was 91.55±26.93 gm/m2, and in group –II it is 77.4±21.7 gm/m2 and it is statistically significant.

The study done by Sedighi O *et al*., (2015), showed that the mean LVMI in CKD patient group was 118.73±13.57gm/m2, and in non-CKD group 92.76±8.34 gm/m2 and the difference was significant statistically [13]. A study done by Sambi RS on 2011, showed that the mean LVMI in control group was 76.62±10.97 gm/m2, and in mild to moderate CKD group it was 114.9±15.2 gm/m2. The finding of this study also in favour of their study as it shows there is increased LVMI in CKD group. But the difference of this study to their study in respect to LVMI (in both the normal population and the CKD group) is a unique finding of this study. The mean EF in group-I patient was 62.96±4.03% and in group-II patient it is 64.9±3.2%, which is statistically significant. In the previously mentioned study, they found EF of 42.66±8.23% in CKD patients and 57.92±7.31% in non-CKD group and it was statistically significant. This difference may be explained by sample size difference, and doing echocardiography in different hands in this study. So it can be said that with the progression of CKD stages beta2 microglobulin level raises significantly in the plasma of CKD patients and the cardiac function also declines.

CONCLUSION

As there is high beta2 microglobulin level seen in CKD non dialytic group of patients and also cardiac performance factors are statistically significantly decreased from the control group, so it can be said that –high plasma beta2 microglobulin level may be associated with decreased cardiac function in CKD patients.

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