ORIGINAL ARTICLE

CORRELATION OF BETA 2 MICROGLOBULIN WITH SERUM CREATININE AND CREATININE CLEARANCE IN PATIENTS WITH DIFFERENT LEVELS OF RENAL FUNCTION

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ABSTRACT

Background: Chronic kidney disease is a major health problem in Pakistan. Serum creatinine is the most common test used to assess renal function. This study was aimed to evaluate the levels of β_2 Microglobulin and creatinine in individuals with different levels of renal function and to see the correlation between these biomarkers.

Material & Methods: Total subjects included in the study were 88; 50 males and 38 females, of 30-60 years age, selected randomly from Sheikh Zayed Hospital Lahore. Creatinine clearance was calculated from serum creatinine and 24 hours urinary volume and urinary creatinine for all study subjects and they were divided into 4 groups on the basis of creatinine clearance.

Results: Serum and urinary β_2 Microglobulin levels were found to be raised in both male and female patients of all groups, while serum creatinine levels were in normal range in patients with creatinine clearance above 60 ml/min. Both β_2 Microglobulin and serum creatinine levels were increased in parallel with the severity of renal disease. It was found that serum and urinary β_2 Microglobulin had a positive correlation with serum creatinine in all groups. β_2 Microglobulin showed negative correlation with creatinine clearance in all groups.

Conclusion: β_2 Microglobulin correlates more closely with different levels of renal functions. It shows positive correlation with serum creatinine and negative correlation with creatinine clearance.

KEY WORDS: β_2 Microglobulin, Serum creatinine, Creatinine clearance, Renal function.

INTRODUCTION

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome.[1] Creatinine is a breakdown product of creatine phosphate in the muscles. Creatinine is transported through the bloodstream to the kidneys.[2] Serum creatinine is the most commonly used test to assess renal function.[3] The National Kidney Disease Education Program recommends calculating glomerular filtration rate (GFR) from serum creatinine concentration.[4] The diagnosis of renal failure is usually suspected when serum creatinine is greater than the upper limit of normal. In chronic renal failure, an eventual reduction occurs in the excretion of creatinine by both the glomeruli and the tubules. Creatinine values may alter as its generation may not be simply a product of muscle mass but influenced by muscle function, composition, activity, diet and health status.[5] The increased tubular secretion of creatinine in some patients with kidney dysfunction could give false negative value.[6]

The impaired renal functions are mainly reflected by the laboratory detection of serum creatinine, which is not sensitive enough to detect early change of renal function, when active management is important.[7] Creatinine reflects renal filtering capacity, which is not sensitive to acute or chronic kidney injury until it is substantial enough to compromise the filtering ability.[8] Recently it has been postulated that a substantial number of patients have evidence of tubular

injury without significant changes in their serum creatinine.[9]

Creatinine clearance (Cr.Cl) is the volume of plasma cleared of creatinine per unit time and is a useful measure for approximating the GFR. However, the creatinine clearance systematically overestimates the GFR due to secretion of creatinine by the renal tubules.[10] By measuring the amount of creatinine excreted in the urine over 24 hours and serum creatinine, the creatinine clearance may be calculated by the formula.

$$Cr.Cl = (uCr \times uV) / (sCr \times 1440).$$[11]

Cr.Cl is Creatinine clearance in ml/min, uCr is Urine Creatinine in mg/dl, sCr is Serum creatinine in mg/dl, uV is 24 hour urine volume in ml and 1440 represents number of minutes in 24 hours.

β_2 Microglobulin is a non-glycosylated protein. In the system, it possesses the negative charge.[12] β_2 Microglobulin is a component of MHC class 1 molecules, which are present on almost all cells of the body except red blood cells. β_2 Microglobulin is generally required for the transport of MHC class I heavy chains from the endoplasmic reticulum to the cell surface.[13,14] β_2 Microglobulin is filtered by the glomerulus, absorbed and catabolised by the proximal tubules. Clinically the appearance of significant amount of this protein in urine is one of the earliest sign of almost all renal diseases.[15] Serum creatinine is affected by factors other than GFR, in particular muscle mass and meat intake. β_2 Microglobulin is released at constant rate in normal subjects, readily filters through the glomerular capillary wall, over 99.9% being reabsorbed and catabolised in proximal tubules with virtually no return of the filtered protein to the circulation. β_2 Microglobulin is therefore theoretically a highly suitable biomarker of renal dysfunction.[16]

The current study was designed to determine the values of these biomarkers in patients with different levels of renal functions and find out the correlation between serum and urinary β_2 Microglobulin, serum and urinary creatinine, blood urea nitrogen and creatinine clearance in patients with different levels of renal function.

MATERIAL AND METHODS

It was a cross-sectional study. Both male and female (88 in number), subjects between the ages of 30 to 60 years; suffering from different levels of renal dysfunction were selected from the Sheikh Zayed Hospital, Lahore. Diagnosed cases of end stage renal disease (ESRD), patients on maintenance hemodialysis and renal transplant were excluded from the study. Pregnant females and individuals with any other systemic disease like malignancy, leukemia, lymphoma and multiple myeloma were also excluded from the study. On the basis of creatinine clearance, the patients were divided into 4 groups. All patients participated willingly. A written research participant consent form was filled by each study participant to undergo tests. History, demographic information and biochemical results of the patients were recorded. A 6-8 ml blood sample was collected in disposable syringes from peripheral vein which was allowed to clot for 25 to 30 minutes at room temperature (37°C), then centrifuged at 3000 RPM for 3 minutes and clear serum obtained was poured in tubes and kept frozen at -20°C for estimation of serum β_2 Microglobulin, serum creatinine and blood urea nitrogen. Twenty-four hour urine samples were collected in plastic containers. Urine was centrifuged to obtain clear supernatant that was stored at -20°C for estimation of β_2 Microglobulin and creatinine. Creatinine and blood urea nitrogen were determined on chemistry auto analyzer, while Serum and urinary β_2 Microglobulin was determined by Enzyme Linked Immunosorbent Assay (ELISA). All data were entered and analyzed through SPSS version 15. Results of serum and urinary Beta 2-Microglobulin, Serum and Urinary Creatinine and Blood Urea Nitrogen were expressed as Mean+SEM for each group. ANOVA technique was used for the comparison of serum and urinary β_2 Microglobulin, Serum Creatinine, and Blood Urea Nitrogen of all the groups. PosthocTukey's test was used for group comparison. Pearson correlation coefficient was utilized to see the correlation between different markers. A 'p' value of less than 0.05 was considered statistically significant.

RESULTS

The results are given below in tables 1 to 6.

Table 1: Gender distribution of patients in different groups.

Group	Male patients	Female patients	Total
1	10	6	16
2	4	6	10
3	10	12	22
4	26	14	40
Total	50	38	88

Table 2: Comparison of serum creatinine, β_2 Microglobulin (MG) blood urea nitrogen (BUN) and creatinine clearance in male patients of different groups.

Groups	Serum creatinine (mg/dl)	Serum β2MG (μg/ml)	BUN (mg/dl)	Creatinine clearance (ml/min)
Group 1 (n=10)	1.25±0.06	5.77±0.29	17.70±0.97	110.09±3.49
Group 2 (n=4)	1.43±0.28	6.24±0.14	20.50±4.05	69.90±3.56
Group 3 (n=10)	1.88±0.30	6.29±0.15	26.70±3.96	44.80±1.65
Group 4 (n=26)	4.75±0.62	9.63±0.58ab	79.50±8.58	11.22±1.40

Values are Mean± SEM.

Table 3: Comparison of serum creatinine, β_2 Microglobulin, blood urea nitrogen and creatinine clearance in female patients of different groups.

Groups	Serum creatinine (mg/dl)	Serum β_2 Microglobulin (μg/ml)	Blood urea nitrogen (mg/dl)	Creatinine clearance (ml/min)
Group 1 (n=6)	0.90±0.13	5.08±0.76	13.00±1.91	124.38±4.35
Group 2 (n=6)	0.98±0.07	5.84±0.20	14.00±1.53	71.12±2.61
Group 3 (n=12)	1.01±0.07	5.88±0.12	14.25±1.07	48.22±1.77
Group 4 (n=14)	2.12±0.25	6.19±0.45	41.07±4.73	18.04±1.76

Values are Mean± SEM.

Table 4: Comparison of urinary β_2 Microglobulin and urinary creatinine in male patients of different groups.

Groups	Urinary β_2 MG(μg/ml)	Urinary Creatinine(mg/dl)
Group 1 (n=10)	1.82±0.51	114.86±17.86
Group 2 (n=4)	2.63±0.48	54.00±5.80
Group 3 (n=10)	5.56±0.71	45.14±7.78
Group 4 (n=26)	6.91±0.43	42.77±3.74

Values are Mean± SEM

Table 5: Comparison of urinary β_2 Microglobulin and urinary creatinine in female patients of different groups.

Groups	Urinary β_2 Microglobulin(μg/ml)	Urinary Creatinine((mg/dl)
Group 1 (n=6)	1.05±0.07	83.62±10.68
Group 2 (n=6)	2.58±0.27	86.88±14.78
Group 3 (n=12)	3.03±0.15	47.36±8.04
Group 4 (n=14)	4.91±0.46	31.74±3.25

Values are Mean± SEM.

Table 6: Correlation of serum β_2 Microglobulin with serum creatinine, blood urea nitrogen and creatinine clearance. Coefficient of correlation (r) is given.

Parameter correlated	Group 1		Group 2		Group 3		Group 4	
	Male (n=10) (r)	Female (n=6) (r)	Male (n=4) (r)	Female (n=6) (r)	Male (n=10) (r)	Female (n=12) (r)	Male (n=26) (r)	Female (n=14) (r)
Serum β_2 Microglobulin with creatinine	0.881**	0.920**	0.209	0.040	0.299	0.184	0.794**	0.943**
Serum β_2 Microglobulin with BUN	0.842**	0.830*	0.124	0.056	0.318	0.207	0.864**	0.941**
Serum β_2 Microglobulin with Cr.Cl	- 0.241	- 0.084	- 0.68	- 0.521	- 0.41	- 0.147	- 0.74**	- 0.377

*p<0.05, **p<0.01

DISCUSSION

Various studies have been conducted to find out the biochemical markers which could play an important role in diagnosis of different renal diseases, assessment of the associated risk and adopting therapy. From these studies, it has been speculated that the appearance of significant amount of proteins in urine is one of the earliest sign of almost all renal diseases. The current study is unique that it was conducted on 88 individuals (50 males and 38 females) between the ages of 30 to 60 years with different levels of renal function and suffering from different renal problems. It may be interpreted from these results that serum creatinine is a poor marker in assessing early renal damage as it is influenced by muscle mass, gender, age, race and medications and is often not elevated until the injury is well established. Moreover, serum creatinine level reflects renal filtering capacity, which has a lot of reservation and is therefore not sensitive to acute or chronic kidney injury until it is substantially enough to compromise the filtering ability. Serum creatinine also does not reflect any renal damage in early stage of diabetes when kidneys are hyper functional due to initial hyperglycemia, leading to increase in the kidney size and higher glomerular filtration rate. Mean serum creatinine in both male and female patients showed inverse correlation to creatinine clearance in all groups. In group 3 and 4, serum creatinine was above the normal, showing renal injury. From these results, it is obvious that serum creatinine is a late marker of renal injury. It does not show early renal damage. In contrast to creatinine, both serum and urinary β_2 Microglobulin values were above the normal in both male and female patients of group 1 and 2. These results indicate that β_2 Microglobulin is more sensitive and accurate biomarker for the assessment of renal functions as compared to serum creatinine. The most probable reason for this could be that South Asians have different diet and muscle mass as compared to Caucasians and creatinine is influenced by these factors. Tazeen et al[16] reported similar results. High values of β_2 Microglobulin in group 1 patients could also be due to any subclinical acute phase disease, as β_2 Microglobulin is released in high amount in acute inflammatory conditions. It was depicted that β_2 Microglobulin correlates more closely to glomerular filtration rate in all different levels of renal functions in different groups of patients as compared to creatinine. β_2 Microglobulin showed positive correlation with creatinine and blood urea nitrogen in all groups of patients while both β_2 Microglobulin and creatinine showed inverse correlation to creatinine clearance in both male and female patients of all four different groups. The consistent negative correlation between β_2 Microglobulin and creatinine clearance, indicates the importance of β_2 Microglobulin in diagnosing renal damage at any level. Measuring β_2 Micro-globulin concentrations is a simple and accurate method of detecting minor degrees of renal damage and monitoring the effects of treatment.

CONCLUSIONS

Serum and urinary β_2 Microglobulin has highly significant positive correlation with both serum creatinine and blood urea nitrogen in all groups of patients. A negative correlation exists between serum and urinary β_2 Microglobulin and creatinine clearance in both male and female patients in all groups.

It is suggested to plan a population based study with larger numbers of individuals having specified race, gender, body mass index and nutritional parameters, so that β_2 Microglobulin can be identified as independent biomarker for the assessment of renal functions.

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