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Plasma beta2 microglobulin as a marker of progression in chronic Kidney disease patients

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ABSTRACT

Chronic kidney disease (CKD) is a world-wide public health problem with adverse outcomes of kidney failure. Early diagnosis and treatment may delay or even prevent the onset of nephropathy in CKD. The measurement of glomerular filtration rate (GFR) is the gold standard for the assessment of renal function. Beta 2 microglobulin has a renal handling compatible with that of an "ideal" marker of GFR. In fact, they are cleared by the plasma through free glomerular filtration, subsequent complete tubular resorption, and degradation inside tubular cells. As a consequence, their serum concentrations increase progressively with the reduction of GFR. The current study was designed to determine the values of this biomarker in patients with different levels of renal dysfunctions and find out the correlation between serum B2 Microglobulin, serum creatinine, blood urea nitrogen and glomerular filtration rate in patients with different levels of renal dysfunction. In this study we found that the levels of serum B2 Microglobulin are highly associated with renal impairment in CKD stages, its concentrations significantly increased from stage 1 to 5 and that these levels progressively increase with decreasing GFR.

Keywords: B2 Microglobulin, Serum creatinine, Creatinine clearance, Renal function.

INTRODUCTION

Early detection of renal disease and screening for early impairment of renal function could allow to slow the rate of progression of the impairment of renal function in chronic kidney disease (CKD) patients (Middleton RJ et al., 2006) the measurement of glomerular filtration rate (GFR) is the gold standard for the assessment of renal function. GFR can be measured as the clearance of inulin or other suitable tracers, like 99mTc-DTPA. None of these methods is adequate for routine clinical use or for screening purposes (Prigent A et al., 2007) 24-hour creatinine clearance (24h-CCr) is frequently used for the evaluation of renal function. However, 24h-CCr lacks both precision and accuracy furthermore due to the necessity of a 24 hour urine collection, it is inadequate for screening studies (Donadio C et al., 1997) The major limitation of serum creatinine (SCr) is its low sensitivity as indicator of early impairment of GFR, since SCr overcomes the upper limit of reference range only in patients at stages ≥ 3b (GFR<45 mL/min/1.73 m2). Furthermore, SCr, besides the level of GFR, is influenced by the amount of muscle mass and, as a consequence, by age, gender and nutritional status of patients (Donadio C et al., 2001)

Beta2 Microglobulin is known to be a surrogate marker for the concentration and removal of other middle-molecular-weight uremic toxins in dialysis patients. Predialysis serum Beta2 Microglobulin predicted mortality, with an 11% increase in mortality for each 10mg/l increase in Beta2 Microglobulin level-even after adjustment for years on dialysis and residual kidney function(Cheung AK et al.,2006)Beta2 Microglobulin is a non-glycosylated protein. In the system, it possesses the negative charge and it is a component of MHC class 1 molecules, which are present on almost all cells of the body except red blood cells (Aksun S Appakan et al.,2004) Beta 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

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proximal tubules with virtually no return of the filtered protein to the circulation, therefore theoretically it is a highly suitable biomarker of renal dysfunction(Jafar TH et al.,2005)

PATIENTS AND METHODS

Patients:

The study was conducted at AlexandriaUniversity Hospitals, Alexandria, Egypt from September 2014 to December 2015. 180 subjects, they were divided into 6 groups according to different stages of CKD and control group.

Exclusion criteria:

Lymphoproliferative (chronic lymphocytic leukemia, lymphomas, and multiple myeloma), solid malignancies (breast, lung, gastrointestinal, and nasopharyngeal carcinomas),Recent administration of potentially nephrotoxic drugs(amino-glycosides, iodinated contrast media and platinum 20 based chemotherapy),Chronic infections (tuberculosis, chronic osteomyelitis and patients with primary amyloidosis),Hepatitis, sarcoidosis, Crohn's disease , vasculitis and Autoimmune diseases.

Methods:

The Beta 2 Microglobulin ELISA is intended for the quantitative determination of Beta 2 Microglobulin in human serum. This assay is for use as an aid in the diagnosis of kidney disease.The ORGENTEC Beta 2 Microglobulin ELISA test is based on the principle of highly putified anti-human- Beta 2 Microglobulin antibodies are bound to microwells. Beta 2 Microglobulin, if present in diluted serum or urine, bind in the microwells. Washing of the microwells removes unreactive serum components. Horseradish peroxidase (HRP) conjugated anti-human Beta 2 Microglobulin immunologically bind to the bound patient Beta 2 Microglobulin forming a conjugate/ Beta 2 Microglobulin /antibody complex. Washing of the microwells removes unbound conjugate. An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue color. The addition of an acid stops the reaction forming a yellow end-product. The intensity of this yellow color is measured photometrically at 450 nm. The amount of colour is directly proportional to the concentration of Beta 2 Microglobulin present in the original sample.

RESULTS AND DISCUSSION

The study was conducted on 180 subjects, which was divided into six groups; group I included 30 normal individuals of average age and sex as a control. Group II include 30 patients with stage1 CKD. Group III include 30 patients with stage2 CKD. Group IV include 30 patients with stage3 CKD. Group V include 30 patients with stage4 CKD. Group VI include 30 patients with stage5 CKD before dialysis. As regard renal function test (Table-1), There was a statistically significant difference between group I and other groups as regard the mean urea ($P<0.001^{*}$). There was statistically significant difference among group I and (IV, V.VI) as

Table-1. Comparison between the different studied groups according to renal function

	Group I (n = 30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	Group V (n=30)	Group VI (n=30)	Test of Sig.
Urea (mg/dl)							
Min. – Max.	11.0 - 64.0	24.0 - 68.0	23.0 - 158.0	30.0 - 169.0	81.0 - 261.0	59.0 - 257.0	$^{KW}\chi^2(p)=120.450^{*}$ ($<0.001^{*}$)
Mean ± SD.	28.27 ± 12.62	49.20 ± 14.61	87.13 ± 39.97	109.20 ± 40.78	167.70 ± 57.73	159.77 ± 53.94	
Median	26.0	49.50	85.50	117.50	151.0	162.0	
$P_{Control}$		**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	
Creatinin (mg/dl)							
Min. – Max.	0.40 - 0.80	0.80 - 1.20	0.90 - 1.80	1.30 - 4.10	2.40 - 8.50	4.50 - 9.90	$F(p)=201.874^{*}$ ($<0.001^{*}$)
Mean ± SD.	0.63 ± 0.13	0.95 ± 0.13	1.22 ± 0.24	2.28 ± 0.72	4.75 ± 1.45	6.96 ± 1.73	
Median	0.70	1.0	1.15	2.10	4.50	6.50	
$P_{Control}$		**0.786**	**0.183**	**<0.001***	**<0.001***	**<0.001***	
GFR (ml/mint)							
Min. – Max.	126.0 - 269.0	90.0 - 113.90	62.50 - 88.80	30.80 - 58.30	13.0 - 28.0	7.50 - 14.30	407.629^{*} ($<0.001^{*}$)
Mean ± SD.	166.36 ± 35.49	101.30 ± 8.47	73.28 ± 7.75	43.26 ± 9.07	19.85 ± 3.62	11.88 ± 2.02	
Median	159.70	100.0	72.0	45.40	19.0	12.35	
$P_{Control}$		**<0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	

F: F value for ANOVA test
Sig. bet. grps was done using Post Hoc test (Tukey)
KW: Kruskal Wallis test
Sig. bet. grps was done using Mann Whitney
$P_{Control}$: p value for comparing between control and each other group
*: Statistically significant at $p \leq 0.05$

regard the mean creatinine in which (P<0.001*). There was a statistically significant difference between group I and other groups as regard the mean GFR (P<0.001*).As regard serum electrolyte (Na, K.Ca and Ph). There was a statistically non-significant differences between group I and other groups (Table 2). As regard Beta 2 Microglobulin (Table 3).There was a statistically significant difference between group I and other groups (P<0.001*).Also there was a significant positive correlation between Creatinine ,Urea and Beta 2 Microglobulin in all groups.There was a significant negative correlation between GFR and Beta 2 Microglobulin (Table-4).

Early screening of CKD, allows intervention strategies aimed to reduce or stop the progression of renal disease, is often difficult to achieve. In fact, after the initial kidney damage, subjective symptoms of renal impairment may completely lack in early stages of CKD. A lot of data indicate that overall awareness of CKD in a high risk population is quite low (Saab G et al., 2008) since clinical symptoms are very poor, the screening for CKD is necessarily based on laboratory tests. Urinary findings (proteinuria, albuminuria, or erythrocytes in urinary sediment) are useful markers of renal disease, while they cannot give information about an eventual impairment in GFR. In the last years, the measurement of serum levels of different low molecular weight proteins (LMWP) has been proposed as more sensitive markers of GFR impairment in comparison with SCr. Indeed, different studies did not confirm the superiority of LMWP vs creatinine. Beta 2 Microglobulin is a protein of low relative molecular weight (11800) that is present in small amounts of normal urine, serum, and other biological fluids. It is structurally related to immunoglobulin G and to the cell-surface histocompatibility antigens. It is synthetized by all nucleated cells and is present on their surface. Its biological role remains unclear (Wilson AM et al., 2007).

In this study we found that the levels of serum B2 Microglobulin are highly associated with renal impairment in CKD stages, its concentrations significantly increased from stage 1 to 5 and that these levels progressively increase with decreasing GFR.

The same findings were reported by (Shahjahan et al., 2011), (Omid Sedighi et al., 2009), (Sophie Liabeuf et al., 2012), (Shinkai et al., 2008), (Stephen P. Juraschek et al., 2003) and (Trailin A. V et al., 2011).

On the contrary with our study (Carlo Donadio et al., 2001) reported that LMWP, namely cystatin (Cys), beta-2 microglobulin and beta tracin protein (BTP) sensitivity as indicators for an early impairment of GFR is not higher than that of SCr, while their analytical procedure is more complex and expensive than that for SCr.

Table-2. Comparison between the different studied groups according to electrolytes

	Group I (n = 30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	Group V (n=30)	Group VI (n=30)	F (p)
Na (mmol/l)							
Min. – Max.	131.0 - 141.0	124.0 - 142.0	125.0 - 140.0	126.0 - 149.0	126.0 - 141.0	113.0 - 143.0	0.965 (0.441)
Mean ± SD.	135.70 ± 2.32	133.67 ± 4.26	135.03 ± 3.70	134.97 ± 5.09	134.0 ± 4.69	133.40 ± 8.21	
Median	136.0	135.0	136.0	134.50	133.50	137.0	
$P_{Control}$		**0.625**	**0.996**	**0.993**	**0.781**	**0.490**	
K (mmol/l)							
Min. – Max.	3.50 - 5.80	2.80 - 6.50	3.30 - 6.10	3.90 - 5.60	3.20 - 7.10	3.30 - 6.50	0.713 (0.614)
Mean ± SD.	4.31 ± 0.57	4.33 ± 0.88	4.40 ± 0.71	4.62 ± 0.44	4.37 ± 0.89	4.48 ± 0.85	
Median	4.20	4.15	4.10	4.60	4.50	4.60	
$P_{Control}$		**1.000**	**0.997**	**0.586**	**0.999**	**0.953**	
Ca (mg/dl)							
Min. – Max.	7.50 - 9.50	6.70 - 9.60	7.40 - 9.60	7.10 - 9.0	7.0 - 9.0	5.50 - 9.30	2.651* (0.024*)
Mean ± SD.	8.40 ± 0.51	8.36 ± 0.60	8.37 ± 0.45	8.20 ± 0.49	8.20 ± 0.53	7.93 ± 0.87	
Median	8.45	8.30	8.30	8.20	8.20	8.15	
$P_{Control}$		**1.000**	**1.000**	**0.792**	**0.792**	**0.029***	
Ph (mg/dl)							
Min. – Max.	1.40 - 5.50	2.50 - 5.20	2.40 - 6.0	2.10 - 6.0	2.60 - 7.60	3.10 - 8.0	9.573* (<0.001*)
Mean ± SD.	3.79 ± 1.10	3.70 ± 0.66	4.31 ± 0.90	4.0 ± 1.14	4.53 ± 1.10	5.30 ± 1.29	
Median	380	3.50	4.30	3.70	4.50	5.10	
$P_{Control}$		**1.000**	**0.404**	**0.974**	**0.073**	**<0.001***	

F: F value for ANOVA test
Sig. bet. grps was done using Post Hoc test (Tukey)
$P_{Control}$: p value for comparing between control and each other group
*: Statistically significant at p ≤ 0.05

Table-3. Comparison between the different studied groups according to Serum B2M (µg/mL)

	Group I (n = 30)	Group II (n=30)	Group III (n=30)	Group IV (n=30)	Group V (n=30)	Group VI (n=30)	$KW_{\square}^2$ (p)
B2M (µg/mL)							
Min. – Max.	3.30 - 12.50	3.90 - 13.10	3.40 - 19.50	6.40 – 23.10	9.40 - 14.80	11.10 - 14.90	73.075* (<0.001*)
Mean ± SD.	6.23 ± 2.58	8.90 ± 2.96	11.02 ± 4.31	11.95 ± 4.13	12.44 ± 1.16	12.77 ± 1.22	
Median	5.55	9.75	11.25	11.25	12.35	12.80	
$p_{Control}$		**0.001***	**<0.001***	**<0.001***	**<0.001***	**<0.001***	

KW: Kruskal Wallis test
Sig. bet. grps was done using Post Hoc test (Tukey)
$P_{Control}$: p value for comparing between control and each other group
*: Statistically significant at p ≤ 0.05

Table-4. Correlation between Serum B2M (µg/mL) and different parameters in each group

	B2M (µg/mL)											
	Group I		Group II		Group III		Group IV		Group V		Group VI	
	r_s	p	r_s	p	r_s	p	r_s	p	r_s	p	r_s	p
Urea (mg/dl)	0.488*	0.006*	0.589*	0.001*	0.727*	<0.001*	0.726*	<0.001*	0.198	0.295	-0.168	0.375
Creatinin(mg/dl)	0.736*	<0.001*	0.661*	<0.001*	0.543*	0.002*	0.808*	<0.001*	0.629*	<0.001*	0.399*	0.029*
GFR (ml/mint)	-0.815*	<0.001*	-0.554*	0.001*	-0.450*	0.013*	-0.690*	<0.001*	-0.440*	0.015*	-0.554*	0.001*

r_s: Spearman coefficient
*: Statistically significant at p ≤ 0.05

CONCLUSION

In conclusion, Serum levels of B2 Microglobulin are significantly higher in all CKD patients compared to the healthy controls and it increases with progression of CKD.There is a strong negative correlation between the eGFR and the B2 Microglobulin level in CKD patients so B2 Microglobulin is theoretically a highly suitable biomarker of renal dysfunction.

Conflict of Interests

Authors declare that there is no conflict of interests regarding the publication of this paper.

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