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B2-Microglobulin Post Kidney Transplantation as A Predictor of Subsequent Kidney Allograph Dysfunction

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ABSTRACT

Background: Long-term outcome in renal transplantation is heterogeneous, and predicting success is challenging. Serum β_2-microglobulin (β_2MG), a novel marker of kidney function, predicts mortality and kidney failure in the general population, and its elevation following transplantation is a marker of acute rejection.

Objective: To determine whether serum beta-2-micro-globulin one three-year post-transplant period could predict the decline in GFR over a follow-up period of six months.

Patients and methods: This study was carried out at the National Institute of Nephrology and Urology, Cairo, Egypt. The patients were subjected to different demographic, clinical, biochemical, ultrasonographic, and endoscopic findings. In this study, 42 primary kidney transplant recipients were included.

Results: The results showed a significant increase in serum β_2-microglobulin level between renal transplant recipients with unstable kidney functions in comparison to renal transplant recipients with stable kidney function. The results showed serum β_2-microglobulin level could be a good predictor of renal graft outcomes. Measurements of serum levels of beta 2 micro-globulin could be more sensitive and more specific than serum creatinine as renal function tests for early prediction of graft dysfunction.

Conclusion: In this study, we found an association between serum level of β2MG in the late post-transplant period and a subsequent decline in kidney allograft function within a short time-frame. The overall results show that a higher serum level of β2MG after a single measurement at different intervals of the late post-transplant period independently predicts the lower eGFR. Thus, higher serum β2MG is a risk factor for graft function, particularly with longer follow-up.

Keywords: B2-Microglobulin; Kidney Transplantation; GFR.

INTRODUCTION

Kidney transplantation is the most effective method of treatment for patients with end-stage renal disease [(1)]. At present, the rate of one-year kidney allograft survival exceeds 95%, and the preservation of allograft function in the late period after transplantation has become the main challenge [(2)].

Identification of patients at risk for kidney graft failure beyond the first post-transplant year is a prerequisite for developing strategies for saving graft function and improving its survival [(3)]. Many recent studies have focused on higher serum creatinine and lower glomerular filtration rate (GFR) within the first post-transplant year as surrogate predictors of inferior graft survival [(3, 4)].

B2-microglobulin (β2MG) is a membrane protein associated with class I major histocompatibility complex proteins and is, therefore, found on the surface of all nucleated cells. Under physiological conditions, β2MG is produced at a constant rate and is eliminated through the kidney. The low molecular weight (11.800Da) allows β2MG to pass through it. Identification of patients at risk for kidney graft failure beyond the first post-transplant year is a prerequisite for developing strategies for saving graft function and improving its survival [(3)].

Several authors reported that measurement of the serum β2MG concentration in native kidney diseases estimates GFR as serum creatinine does [(5)] and even supersedes it [(6)].

Astor *et al.* have recently demonstrated that high serum β2MG at discharge predicted kidney graft loss [(7)], but detailed retrospective information might not be available for all patients. The association between serum β2MG and the rate of decline in kidney allograft function remains obscure [(8)].

AIM OF WORK

This work aims to determine whether serum beta-2-micro-globulin one three post-transplant period could predict the decline in glomerular filtration rate (GFR) over a follow-up period of six months.

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PATIENTS AND METHODS

This study was carried out in the National Institute of Nephrology and Urology. The patients were subjected to different demographic, clinical, biochemical, ultrasonographic findings. In this study, 42 primary kidney transplant recipients were included. Group (A) included 21 recipients with stable kidney functions and group (B) included 21 recipients with unstable kidney functions in the form of high serum creatinine, with a single measurement of B2 Microglobulin one time. If we found elevated B2 Micro-globulin level among the group (A), follow up for six months for detecting any change in estimated glomerular filtration rate (eGFR).

Ethical consideration and Written informed consent:

Approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation.

Inclusion criteria:

1. The adult kidney allograft recipient, male or female, with primary transplantation from living related or unrelated donor. All recipients are taking conventional triple therapy.
2. Average ischemia time, smooth post-operative period, not diabetic, compliant patient, no graft artery stenosis.

Exclusion criteria:

Regular dialysis, acute kidney injury, diseases of the immune system, solid tumors, diabetic, children below 18 years, elder above 60 years, non-complaint patients, graft artery stenosis, prolonged post-operative time, not first transplantation, patients are taking induction therapy.

All patients were subjected to the following:

1-Complete history taking.

2-Complete clinical and physical examination.

3-Laboratory Investigations: In the form of:

- CBC (Complete Blood Pictures).
- KFT (kidney function test).
- Serum B2 Microglobulin.
- Urine Protein / Creatinine Ratio.
- Urine analysis.

Study design:

We choose 21 patients with stable graft function, called group A. We choose 21 patients with unstable graft function with eGFR less than 80 ml/min/1.73m^2. A single measurement of B2 Microglobulin one time. Among group A, if elevated B2 Microglobulin level was found, follow up for six months for detecting any change in eGFR.

Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing two means.
- Chi-square (x^2) test of significance was used to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered highly significant.
  - P-value >0.05 was considered insignificant.

RESULTS

Table (1): Age and sex distribution

			Group A	Group B	t	P
Age			**35.61±8.75**	**34.04±8.09**	**0.604**	**0.549**
Gender	**Female**	**N**	**8**	**6**	**1.82**	**0.398**
		%	**38.1%**	**28.6%**		
	Male	**N**	**13**	**15**		
		%	**61.9%**	**71.4%**		
Total		**N**	**21**	**21**		
		%	**100.0%**	**100.0%**		

There was no significant difference between the two groups.

Table (2): B2 distribution

	Group A	Group B	t	P
B2 microglobulin	1.76±0.52	6.34±2.11	-6.427	0.00**

Group B sig higher.

Table (3): ROC Curve for cutoff of group B

	Cutoff	P	95% Confidence Interval	
			Lower Bound	Upper Bound
0.861	>3.05	0.00**	0.715	1.000

Sig area under curve and cutoff >3.05.

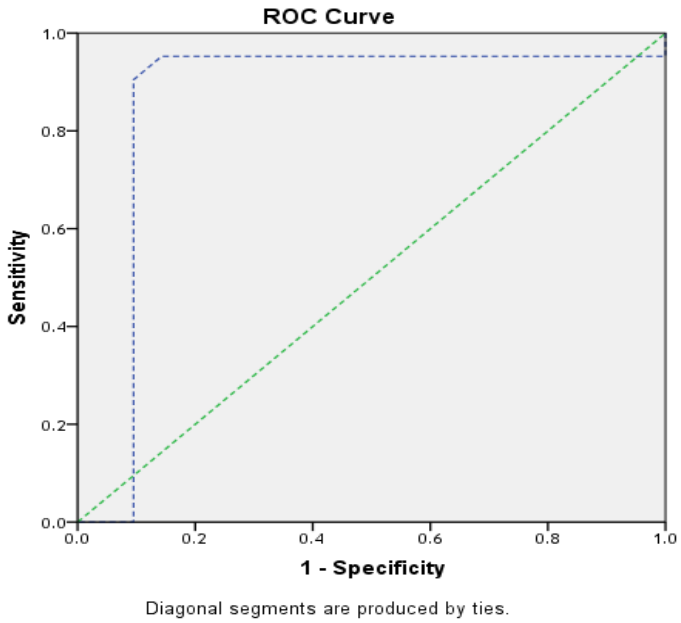

Fig. (1): ROC Curve for the cutoff of group B.

Table (4): Association and agreement

			Group		Total	X^2	P	Kappa agreement
			Group A	Group B				
B2	**<3.05**	**N**	**19**	**2**	**21**	**27.52**	**0.00****	**0.77**
		%	**90.5%**	**9.5%**	**50.0%**			
	>3.05	**N**	**2**	**19**	**21**			
		%	**9.5%**	**90.5%**	**50.0%**			
Total		**N**	**21**	**21**	**42**			
		%	**100.0%**	**100.0%**	**100.0%**			

Significant association and agreement with sensitivity 90.5% and specificity 90.5%

Table (5): Comparison between 2 cases deteriorate and 19 stable cases among group A regard age and sex

			Deteriorated	Not	t/X^2	P
Age			21.5±0.7	37.1±7.78	-2.769	0.012*
Gender	**Female**	**N**	0	8	1.36	0.24
		%	0.0%	42.1%		
	Male	**N**	2	11		
		%	100.0%	57.9%		
Total		**N**	2	19		
		%	100.0%	100.0%		

Deteriorated cases were significantly younger in age.

Table (6): Comparison between 2 cases deteriorate and 19 stable cases among group A regard LABs

	Deteriorated	Not	t	P
ALT (U/L)	13.5±2.12	14.1±3.2	-0.217	0.831
AST (U/L)	29.5±0.7	29.89±3.07	-0.177	0.861
Albumin (g/L)	4.5±0.7	3.93±0.4	1.774	0.092
PT	12.0±0.0	12.47±0.74	-0.320	0.752
INR	0.95±0.21	0.94±0.08	0.037	0.971
Hb (g/dl)	12.95±0.08	13.68±1.21	-1.755	0.071
Hct	44.5±0.7	45.31±2.16	-0.520	0.609
TLC	5.5±0.7	6.52±1.5	-0.932	0.363
PLT	287.0±9.89	238.9±51.95	4.277	0.001**
Creatinine (mg/dL)	0.95±0.07	0.86±0.21	-0.410	0.687
Urea (mg/dL)	35.0±4.24	31.68±4.0	1.111	0.280

PLT was significantly higher among deteriorated cases

Table (7): Comparison between 2 cases deteriorate and 19 stable cases among group A regard B2

	Deteriorate	Not	t	P
B2 microglobulin	2.8±0.14	1.65±0.57	3.12	0.002*

Deteriorate cases sig higher

Table (8): ROC Curve for detection of cutoff of deterioration

Area	Cutoff	P	95% Confidence Interval	
			Lower Bound	Upper Bound
0.895	>2.3	0.022*	0.757	1.000

Sig area under curve and cutoff >3.05

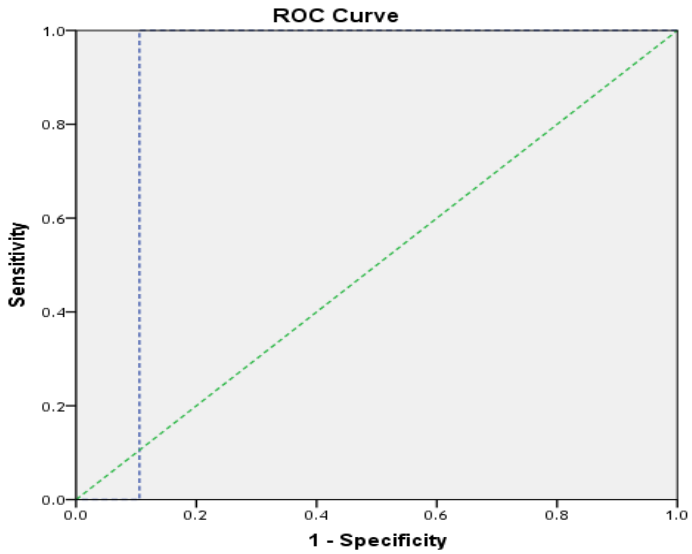

Fig. (2): ROC Curve for detection of cutoff of deterioration.

Table (9): Association and agreement

			Deteriorate		Total	X^2	P	Kappa agreement
			No	Yes				
B2	**<2.3**	**N**	17	0	17	9.39	0.002*	0.67
		%	89.5%	0.0%	81.0%			
	>2.3	**N**	2	2	4			
		%	10.5%	100.0%	19.0%			
Total		**N**	19	2	21			
		%	100.0%	100.0%	100.0%			

Significant association and agreement with sensitivity 100.0% and specificity 89.5%

Table (10): Correlation with B2:

		s_B2micro_globulin
Age (years)	**r**	**-.018-**
	P	**.912**
ALT (U/L)	**r**	**.038**
	P	**.814**
AST (U/L)	**r**	**-.043-**
	P	**.788**
Albumin (g/L)	**r**	**-.036-**
	P	**.822**
PT	**r**	**-.152-**
	P	**.336**
INR	**r**	**-.348-***
	P	**.024**
Hb (g/dl)	**r**	**-.175-**
	P	**.268**
Hct	**r**	**-.585-****
	P	**.000**
TLC	**r**	**-.045-**
	P	**.777**
PLT	**r**	**-.276-**
	P	**.077**
Creatinine (mg/dL)	**r**	**.344***
	P	**.026**
Urea (mg/dL)	**r**	**.737****
	P	**.000**

B2 was significantly positively correlated with Cr and urea but sig negative correlated with INR and HCT

DISCUSSION

Our results revealed that there was no significant difference in the demographic distribution among the studied cases regarding their age and gender in the group (A) with a stable graft function and group (B) with unstable graft function.

These results are in agreement with **Trailin *et al.*** [9] who reported that the majority of patients received a kidney from a living donor have no differences in gender and age.

Our results showed that there was no significant difference in the etiology distribution of renal failure including APKDS, drug abuse, FSGS, HTN, Idiopathic causes, and SLE among the studied cases in the group (A) with a stable graft function and group (B) with unstable graft function. Our results showed that there was a significant increase in the b2M distribution among the studied cases in the group (B) with unstable graft function and group (A) with stable graft function.

These results are in agreement with **Woo *et al.*** [10] who mentioned that Increased serum b2-M levels may reflect either increased synthesis and/or defect of glomerular filtration. Increased urinary excretion reflects primarily defective tubular re-absorption and/or possible increased filtered load. In the case of the transplanted kidney, this increased urinary b2-M excretion would probably indicate proximal tubular damage due to transplant rejection.

Our results are in agreement with **Dieterle *et al.*** [11] who mentioned that β2M is almost exclusively cleared by the kidney, freely filtered by the glomerulus then reabsorbed and metabolized by the proximal tubular cells. It is a sensitive marker of decreased renal filtration or tubular injury

This interesting finding may reflect both renal and non-renal indicator functions of b2M. This molecule may offer a more precise measurement of graft function than serum creatinine, particularly at lower levels of clearance, hence being a more accurate predictor of long-term survival [7].

Serum b2M levels rise as kidney function falls in chronic kidney disease. Several studies in the general population or patients with chronic kidney disease have found that b2M correlates more strongly with directly measured GFR than does serum creatinine [12].

Our results concur with **Keown** [13] who stated that elevated serum b2M levels predict reduced patient survival in the elderly, in uremia, in cardiovascular disease and other chronic disease states.

The attainable results are corresponding to **Poge *et al.*** [14] who mentioned that successful transplantation results in a substantial decrease in b2MG within the first few days, but levels are not

uniformly normalized. B2MG levels remain elevated, or increase after an initial decline, in patients with delayed graft function or acute rejection.

Our results go in the same way with **Dieterle *et al.*** [11] who suggested that β2M levels rise in renal failure, fall rapidly following successful renal transplantation, and have shown a strong correlation with measured GFR.

Contrary to this study**, Sonkar *et al.*** [8] have found that all cases of acute or chronic TR(transplanted rejection) and 42.8% (3/7) of TS cases had raised β2MG, and the remaining 57.1% (4/7) of TS cases of renal transplant had a value < 2 µg/ml. 21.4% of normal healthy controls also had raised β2MG between 2.1 and 10 µg/ml, but none of the normal healthy controls or TS cases had β2MG above 10 µg/ml.

Our results revealed that B2MG was significantly positively correlated with Cr and urea but negatively significantly correlated with INR and HCT.

These results are in agreement with **Trailin *et al.*** [9] who suggested that type of the donor, age and gender of the recipient, characteristics of acute rejection episodes, type of initial graft function, mean arterial pressure, and time after transplantation did not correlate with the serum levels of β2MG. Only serum creatinine concentration, eGFR, and normalized proteinuria are significantly correlated with serum β2MG levels.

Our results regarding the 2 deteriorated cases in comparison with 19 stable cases with graft function in the group (A) showed that the deteriorated cases were significantly younger, associated with idiopathic and PLT was significantly higher among deteriorated cases.

The attained results for the deteriorated cases in the group (A) revealed a significant increase in the values of b2M compared with stable cases in the same group which is (2.8±0.14 versus 1.65±0.57), respectively.

These results concur with **Cheung *et al.*** [12] who observed that a higher concentration of circulating b2M at discharge may indicate increased production due to inflammation. Post-transplant inflammation may be due to pre-transplant conditions, the surgery itself, ischemia-reperfusion injury, the immune response, and agents used to suppress this response. B2MG was substantially increased in hemodialysis where higher levels predicted mortality in the HEMO Study.

Others have found b2M to be increased among individuals with heart disease or peripheral vascular disease. The cross-sectional associations of b2M with higher age, gender sex, race, and history of diabetes and cardiovascular disease give credence to this hypothesis [15].

Furthermore, the fact that b2M predicted events occurring 3 years post-transplant suggests that if the association is due to inflammation the conditions causing increased inflammation are continuous and have long-lasting effects [7].

Measurements of serum levels of beta 2 micro-globulin were more sensitive and more specific than serum creatinine as renal function tests for early prediction of AKI (acute kidney injury) [16].

Contrary to these studies**, Sonkar *et al.*** [8] concluded that Serum Creatinine is a simple, cheaper, and superior test over β2MG in diagnosing TR cases.

Our results regarding Association and agreement showed a significant association and agreement with a sensitivity of 90.5% and specificity 90.5% in the group (A).

Our results are in agreement with **Astor *et al.*** [7] suggested that the associations were observed in patients at every level of eGFR at discharge, although serum b2MG predicted mortality most strongly in those patients with higher eGFR at discharge. In contrast, serum creatinine at discharge was not significantly associated with mortality during follow-up, and the association of discharge serum creatinine with subsequent graft loss was much weaker than that for b2MG.

Our obtainable results regarding some lab parameters distribution showed that the values of HB, HCT, and PLT were significantly higher in group A compared to group B which are (12.84, 45.23, and 243.52 versus 11.21, 37.19 and 198.57), respectively. However, the values of creatinine and urea were significantly lower in group A compared to group B which are (1.2 and 32.0 versus 2.54 and 99.47), respectively.

These results are in agreement with **Trailin *et al.*** [9] who revealed that the main laboratory parameters of graft status (eGFR, and normalized proteinuria) were highly significant in the dysfunction group compared to the group of patients with satisfactory function.

The vagaries of creatinine-based measurements are well known, and simple numerical predictors of fractional increase are hazardous. This hypothesis is certainly amenable to investigation. Additionally, b2MG levels may indicate an increased inflammatory burden related to tissue ischemia, subclinical allograft rejection, or inflammatory injury associated with chronic cardiovascular disease in the setting of chronic uremia [13].

CONCLUSION

In this study, we found an association between serum level of β2MG in the late post-transplant period and a subsequent decline in kidney allograft function within a short time-frame.

The overall results show that a higher serum level of β2MG after a single measurement at different intervals of the late post-transplant period independently predicts the lower eGFR. Thus, higher serum β2MG is a risk factor for graft function, particularly with longer follow-up.

These observations highlight the potential importance of elevated serum β2MG in the late post-transplant period in identifying a group of transplant patients who are at risk for rapid loss of graft function and might benefit from early therapeutic interventions.

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