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Using Serum Beta Trace Protein to Estimate Residual Kidney Function in Hemodialysis Patients

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ABSTRACT

Aim of the work: residual kidney function (RKF) in end stage kidney disease (ESKD) patients contributes significantly to solute clearance. This improves survival as well quality of life in these patients. Kidney Diseases Outcomes Quality Initiative (KDOQI) guidelines suggest that hemodialysis (HD) dose can be safely reduced in those with RKF in the form of residual urea clearance (KRU) of 2 ml/min/1.73 m^2 or more. However, measurement of RKU is difficult as it requires regular inter-dialytic urine collections. Simpler methods for measuring KRU and thus RKF are needed. Beta trace protein (BTP)have been proposed as alternative markers of RKF and RKU. Dialysis specific equations to estimate KRU based on serum BTP wererecentlydeveloped. This study aimed to compare measured KRU using inter-dialytic urine collection and estimated KRU using serum BTP.**Patients and Methods**: we included 60 ESKD patients in this study;they were divided into 2 groups. Group-1(G-1) had daily urine output <500ml and group-2(G-2) haddaily urine output >500ml. We estimated and measured KRU in both groups. Correlation between measured and estimated KRU in each group was done using Pearson correlation coefficient. **Results**: the estimated and measured KRU was strongly correlated in G-1 with r=0.746 at p<0.01 , but it was week in G-2 with r=0.44 and p<0.05.Mean bias between estimated and measured KRU was 0.7 mL/min in G-1. In G-2 the mean bias was -0.54mL/min. **Conclusion**: KRU and thus RKF can be better estimated using serum BTP in patients with urine output >500mL than in patients with daily urine output200-500mL.

Keywords:Hemodialysis,Residual,Kidney,Function,Beta-Trace-Proteins.

INTRODUCTION

Chronic kidney disease (CKD) is a major health issue as it is considered as a major cause of mortality. The risk of mortality increases exponentially with decreasing renal function **(1).**The Kidney Disease Outcome Quality Initiatives (K/DOQI) classifies CKD into 5 groups according to the glomerular filtration rate (GFR).Stage 5 is End Stage Kidney Disease (ESKD) and patients in this stage require renal replacement therapy(RRT) to carry out some functions of the failed kidneys**(2).**

Table1:CKD staging according to K/DOQI(2)

Stage	Description	GFR: ml/min/ m2	Related Items
1	Kidney damage with normal kidney functions	>90	Hematuria,proteinuria, Albuminuria
2	Kidney damage with mild reduction of GFR	60-90	Hematuria,proteinuria, Albuminuria
3	Moderate GFR reduction	30-60	Early renal insufficiency
4	Severe GFR reduction	15-30	Late renal insufficiency
5	Renal failure	<15	End-stage-renal-disease

Once CKD patients approach ESKD they lose ability to remove uremic toxins and maintain body euvolumia. They should be referred to a nephrologist care. The patient and his family should be educated about the possible RRTs which includes hemodialysis(HD), peritoneal dialysis(PD) and renal transplant**(3).**

Hemodialysis(HD) carry out some functions of the kidneys in ESKD patients .It removes many uremic toxins like urea and creatinine, normalize electrolytes such as potassium, calcium and phosphate as well as removing excess fluid gains between sessions also known as ultrafiltration**(4).**

Residual kidney function(RKF) is the remaining minimal GFR in patients diagnosed as ESKD who require RRT.Patients with RKF suffer less adverse cardiovascular and anemia; they also tend to have better mineral and nutritional control**(5).**

RKF is generally expressed as urinary clearance of urea(KRU). Current guidelines recommend assessment of RKF at regular intervals.KRU is included in hemodialysis adequacy if it is >2 ml/min**(6).**

However, there are no simple methods for assessing RKF that are similar to GFR estimation from serum creatinine in non dialysis patients. RKF is assessed by timed 24 to 48 hour urine collection with calculation of KRU. Urine collection is difficult and is prone to errors**(6).**

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Beta trace proteins (BTP) also known as prostaglandin D_2 sythase, is a low molecular weight glycoprotein. Its molecular weight is 23,000 Da and is made of 168 amino acids. BTP is produced mainly in the central nervous system and also by the retina ,kidneys ,testes and heart, but it is exclusively excreted by the kidneys. Serum concentration of the BTP is highly correlated with measured GFR[7].

As HD clearance is minimal for BTP it makes it attractive candidates for measuring RKF. Dialysis specific equation using serum BTP was recently developed to estimate the KRUand thus RKF in HD patients. Bias using this equation was low and precision and accuracy was high[6]. This study aimedto compare KRU estimated from the equation using serum pre-dialysis BTP with KRU measured using serum and urinary urea in two groups of ESKD patients who retain RKF, Group-1(G-1) had urine output <500ml/24 hrs and group-2(G-2) had urine output >500ml/24 hrs.

PATIENTS AND METHODS

This study included 60 ESKD patients on HD at the Dialysis and Nephrology Department of the Italian(Umberto-I) Hospital. The patients were divided into 2 groups. Group-1 (G=1) included patients with daily urine output of >500ml. Group-2 (G-2) included those with urine output from 200-500ml.

Inclusion criteria

1-ESKD patients at least 18 years old

2-Daily passage of urine: >500ml urine in G-1 and 200-500mL in G-2

Exclusion criteria

1-Patients who were recieved previous kidney transplant

2-Patients who were recieved medication containing corticosteriods

Urinary Urea Clearance Measurement and Estimation

The KRU was measured in the interdialytic period which averaged around 44 hours. The patients were asked to collect all urine produced during this inter-dialytic period. Urinary urea nitrogen(UUN) concentration and urine volume was calculated. Serum blood ureanitrogen(BUN) samples were drawn at the end of the preceding HD session and directly before the next HD. We used the mean of these 2 values for the measurement urinary urea clearance calculations as follows:

UUN concentration *Urine Volume /Mean BUN Concentration.

Using serum BTP we estimated the urinary urea clearance using the formula: $69xBTP^{-2.144}x(1.677$ in male) [6]

Serum BTP assay was done by ELISA technique using reagents of BTP provided by Bioneovan Co., LTD, Beijing China. The kit allows determination of BTP concentration in human serum,cell culture supernates and other biological fluids. This test employs a sandwich enzyme immunoassay method for quantities measurement of serum BTP. The samples are requires to be coagulated at room temperature for 10-20 minutes then centrifugated at 2000-3000 rpm for 20 minutes to remove supernatant .Blood samples for serum BTP were taken pre-dialysis immediately before the first HD session.

This study was done after approval of ethical board of Ain Shamns univeristy and an informed written consent was taken from each participant in the study.

Statistical Analysis

We performed a descriptive analysis of the study population as to assess its characteristics to compare it with other HD populations. Correlation between measured urea clearance and serum BTP, serum urea and previous months on dialysis was made.Correlation between measured and estimated KRU in each group was done using Pearson correlation coefficient. Bias and level of agreement between measured and estimated KRU was done using Bland-Altman plot. Bias was calculated as the mean difference between measured and estimated KRU. Comparison between the two groups estimated KRU, and the two groups measured KRU was done using independent T-Test. Level of significance was considered highly significant at $p<0.01$ and significant at $p<0.05$We performed all analyses using SPSS software.

RESULTS

The mean age of all patients was 55.5 years, mean age of G-1 was 54.4, while that of G-2 was 57. Males made 66.7% of all patients and 63% in G-1 and 73% in G-2. Several patients were new dialysis patients and median duration of prior dialysis was 9 months overall, 7months in G-1 and

16 in G-2. Majority of patients didn't know the cause of their kidney disease, but the leading known cause of ESKD was diabetes(26.7%) then hypertension(16.7%) ,obstructive uropathy (6.7%) and glomerulnephritis (3.3%).

Table2: patients characteristics

		All n=60	Group1(n=41)	Group2(m=19)
Age (years)	Mean±SD	55.52 ± 11.20	54.4±8.8	57±12.2
Sex	Female Male	20 (33.3%) 40 (66.7%)	15(37%) 26(63%)	5(27%) 14(73%)
Duration prior of dialysis :months	Median(IQR)	9 (4 – 15)	7(2-13)	16(10-21)
Calcium mg/dl	Mean±SD	8.29±0.8	8.38±-0.86	8.12±0.58
Phosphate mg/dl	Mean±SD	5.22±1.79	5.17±1.73	5.3±1.73
Hemoglobin g/dl	Mean±SD	10.34±1.67	10.6±1.8	9.8±1.15
ALP mg/dl	Mean±SD	161±12	176±14	126±5
Dry Weight (kg)				
Cause of ESKD	Diabetes Glomeruloneph Hypertension Obstructive Unknown/other	16 (26.7%) 2 (3.3%) 10 (16.7%) 4 (6.7%) 28 (46.7%)	11(26%) 2(4.8%) 7(17%) 2(7%) 19(46%)	5(26%) 0(0%) 3(15.7) 2(10.5%) 9(47%)

The KRU was measured using the mean of Pre-dialysis and Post-dialysis BUN , urine volume and UUN. Estimated KRU was measured using serum BTP. Other determinants of measured and estimated KRU are shown below.

Table3: determinant of measured and estimated KRU

		All (n=60)	Group-1 (n=41)	Group-2(n=19)
Serum BTP: mg/l	Mean±SD	5.31 ± 1.07	6.53±1.32	4.73±1.05
Estimated KRU: ml/min	Median(IQR)	2.82 (1.95 – 4.39)	4.02 (1.59-2.3)	1.88 (2.31-5.71)
ID Urine volume : ml	Mean±SD	1072.33 ± 209.98	1250±295	611±177
Urine collection time: hrs	Mean±SD	42.37 ± 4.88	44±5.6	43±2.29
Urine volume:ml/min	Mean±SD	0.45 ± 0.14	0.49±0.16	0.6±0.12
Urine Volume/24hrs:ml	Mean±SD	626.79 ± 154.43	681±156	337±92
Predialysis BUN :mg/dl	Mean±SD	67.25 ± 10.13	64±9.6	71 ± 10
Post dialysis BUN :mg/dl	Mean±SD	25 ± 4.5	24±4.14	26.4±4.7
Serum Creatinine	Mean±SD	8.26±2.05	7.6±1.55	8.46±2.09
UUN: mg/dl	Mean±SD	300.45 ± 57.68	316±60	290±52
Measured KRU: ml/min	Median(IQR)	2.36 (1.67 – 3.64)	3.3 (2.17-4.49)	1.30 (1.08-1.8)

Urine out put correlated positively with estimated and measured KRU in G-1 but with only estimated KRU in G-2. Serum BTP and duration of dialysis correlated negatively with measured and estimated KRU in both groups. Serum BUN and creatinine correlated negatively with estimated KRU while hemoglobin(HB) correlated positively with measured KRU in G-1

Table4: correlations of Group-1

	Estimated KRU: ml/min		Measured KRU: ml/min	
	r	p-value	r	p-value
Urine volume	0.5091	0.0260*	0.12	0.641
Duration prior of dialysis: months	-0.47	0.042*	- 0.57	0.017*
Predialysis BUN	-0.151	0.249	-0.286	0.231
Serum BTP: mg/l	-0.731**	0.001	-0.471*	0.042
HB	-0.277	0.252	-0.343	0.150
Calcium	0.070	0.771	-0.007	0.97
Phosphorous	-0.075	0.077	0.64	0.4
ALP	0.067	0.781	0.372	0.116
Creatinine	-0.038	0.902	-0.486	0.064

Table5: correlations of Group-2

	Estimated KRU: ml/min		**Measured KRU: ml/min**	
	r	**p-value**	**r**	**p-value**
ID Urine Output	0.3173	0.0432*	0.44	0.003**
Duration prior of dialysis: months	-0.508	0.001**	-0.319	0.040*
Predialysis BUN	-0.381	0.013*	-0.298	0.058
Serum BTP: mg/l	-0.812**	0.001**	-0.393*	0.011
HB	0.202	0.283	0.330*	0.035*
Calcium	0.03	.852	-0.134	0.407
Phosphorous	-0.111	0.402	0.13	0.417
ALP	0.072	0.654	0.152	0.340
Creatinine	--0.309*	0.049	-0.149	0.382

A strong positive correlation was found between the estimated and measured KRU in G-1 with correlation coefficient of r=0.741 which was significant at **p** value=<0.01

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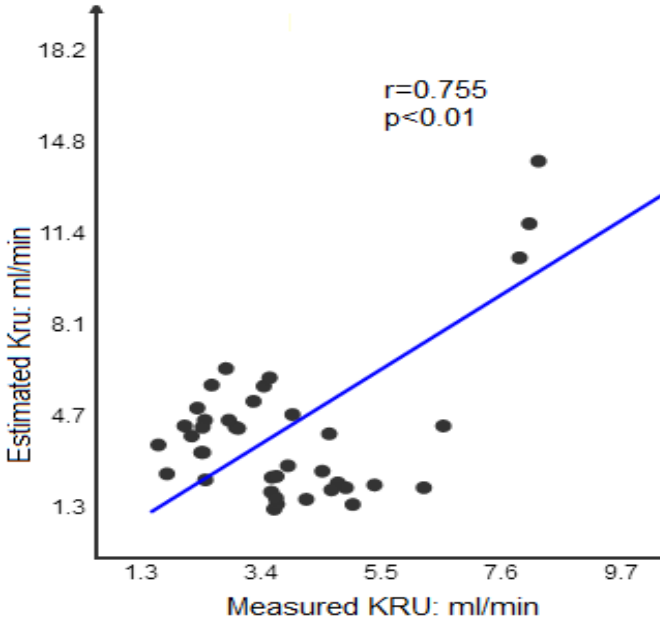

Figure1 :correlation of measured and estimated KRU in G-1

The correlation in G-2 was weekly positive with correlation coefficientr=0.462 and was significant at p-value=<0.05.

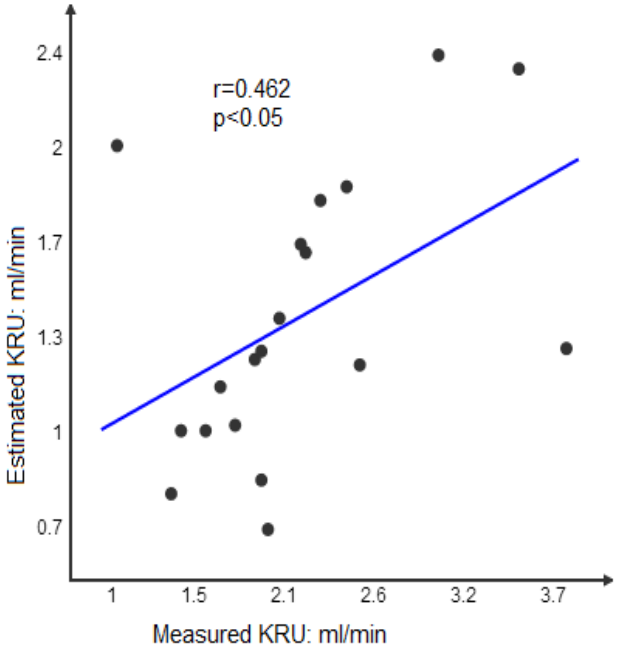

Figure2 :correlation of measured and estimated KRU in G-2

Mean bias between the estimated and measured KRU was 0.7 mL/min with 95% limits of agreement between 3.5mL/min and -1.96mL/min in G-1. In G-2 the mean bias was -0.54mL/min with 95% limits of agreement between 0.75mL/min and -2 mL/min.

Table 6:Bland-Altman plot analysis

	Mean Bias	Upper limit of agreement	Lower Limit of agreement
Group-	0.7	3.5	-1.96
Group-	-0.54	0.75	-2 mL/min

Comparing the estimated KRU between the 2 groups using T-Test showed t value of 3.06 at p<0.01. Comparing the measured KRU between 2 groups showed t-value is 4.5 at p<0.01. There is a highly significant difference between the estimated and measured KRU in two groups.

Table 7: comparison between the two groups

	t-value	p-value
Estimated KRU	3.06	<0.01
Measured KRU	4.5	<0.01

DISCUSSION

We used Pearson correlation to detect the relationship of the measured KRU and estimated KRU. There was strong positive correlation in G-1 with correlation coefficient r=0.741 which is highly significant at P value of p=<0.001 with weak correlation in G-2 ; the correlation coefficient was r=0.462 which was significant at p<0.05.This means that the estimated KRU was better correlated with the measured KRU in patients who had urine output >500ml/min. In another study using BTP to estimate urea clearance the correlation coefficient was r=0.781[8].

Using Bland-Atman plot, mean bias between the estimated and measured KRU was 0.7 mL/min with 95% limits of agreement between 3.5mL/min and 1.96mL/min in G-1. In G-2 the mean bias was -0.54mL/min with 95% limits of agreement between 0.75mL/min and -2 mL/min. Mean bias between the measured and estimated KRU in the **Wong *et al***.cohort was –0.50 ml/min with 95% limits of agreement from –2.03 to1.04 ml/min[8] .

Comparing the estimated KRU between the 2 groups using T-Test showed t value of 3.06 at $p<0.01$. Comparing the measured KRU between the 2 groups showed that t-value was 4.5 at $p<0.01$. There was a highly significant difference between the estimated and measured KRU in the two groups.

CONCLUSION

Residual kidney function is important predictor of mortality and morbidity in ESKD patients. Measuring RKF requires urine collection making it difficult. The equation using BTP to estimate RKU and thus RKF correlated strongly with measured RKU in patients with urine output >500 ml/24 hrs and had mean bias of 0.7mL/min but only week correlation was found in patients with 200-500 mL/24 hrs and the mean bias was 0.54 mL/min. There was also a significant difference between the measured and estimated KRU in both groups.

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