Using Serum Beta Trace Protein To Estimate Residual Kidney Function In Hemodialysis Patients

Thesis

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List of Abbreviations

Abb.	Full term
ACE-I	*Angiotensin convertin enzyme-inhibitor*
ADPKD	*Autosomal dominant polycystic kidney disease*
ARBS	*Angiotensin II receptor blockers*
AVF	*Arterio-venous fistula*
AVG	*Arterio-venous grafts*
B2M	*Beta-2 microglobulin*
BMI	*Body mass index*
BSA	*Body surface area*
BTP	*Beta trace protein*
BUN	*Blood Urea Nitrogen*
CKD	*Chronic kidney disease*
CKD-EPI	*Chronic Kidney Disease-Epidemiology*
CKD-MBD	*CKD mineral bone disease*
CRRT	*Continuous renal replacement*
CSF	*Cerebrospinal fluid*
CT	*Computer tomography*
CVC	*Central veins catheters*
ELISA	*Enzyme-linked immunosorbent assay*
EPO	*Erythropoietin*
ESKD	*End Stage Kidney Disease*
ESRD	*End-stage renal disease*
GFR	*Glomerular filtration rate*
GN	*Glomerulonephritis*
HbA_{1c}	*Hemoglobin A_{1c}*
HD	*Hemodialysis*
HDF	*Hemodiafitration*
HIT	*Heparin Induced thrombocytopenia*
ID	*Inter-dialytic*
K/DOQI	*Kidney Disease Outcome Quality Initiatives*
KDa	*Kilo Dalton*

List of Abbreviations cont…

Abb.	Full term
KRU	*Renal urea clearance*
L-PGDS	*Lipocalin-type prostaglandin D synthase*
MRI	*Magnetic resonance imaging*
NSAIDs	*Non steroidal anti-inflammatory drugs*
PD	*Peritoneal dialysis*
PGD2	*Prostaglandin D2*
PGH2	*Prostaglandin H2*
PTH	*Parathyroid hormone*
RKF	*Residual kidney function*
RKF	*Residual kidney function*
RRT	*Renal replacement therapies*
RTNx	*Renal transplant*
SLED	*Sustained low-efficiency dialysis*
TMP	*Trans-membrane pressure*
UF	*Ultrafiltration*
USRDS	*United States Renal Data System*
UUN	*Urinary urea nitrogen*
WHO	*World Health Organization*

Abstract

In this study we aim to compare the estimated KRU from the equation using serum pre-dialysis BTP with actual KRU measured using serum urea and urinary urea in ESKD patients on regular HD who retain RKF. We divided the patients into 2 groups. Group1(G-1)had urine output >500ml/24 hrs and group2(G-2) had urine output 200-500 ml/24 hrs.

Strong correlation between estimated and measured KRU in G-1 with correlation coefficient of r=0.741 which is highly significant at $p<0.001$. In G-2 the correlation was week at r-0.462 and significant at $p<0.05$. Mean bias between 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. Comparing the estimated KRU in the 2 groups showed t value of 3.06 at $p<0.01$. Comparing the measured KRU in 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.

In conclusion, serum BTP can be used to estimate RKF and RKU without urine collection. However the estimation may become better in patients with urine output more than 500ml/24 hrs than those with urine output 200-500 mL/24 hrs.

keywords: *Parathyroid hormone- Renal replacement therapies- Renal transplant- Sustained low-efficiency dialysis*

INTRODUCTION

Chronic kidney disease (CKD) is a major health issue as it is considered a major cause of mortality with around 864 226 death worldwide or 1.5% of total death was related to CKD in 2012 ***(World Health Organization (WHO) mortality estimates, 2016).*** The risk of mortality increases exponentially with decreasing renal function ***(Tonelli et al., 2006)***.

The Kidney Disease Outcome Quality Initiatives (K/DOQI) classifies CKD into 5 groups according to glomerular filtration rate (GFR) as follow:

Table (1): CKD classification by K/DOQI guidelines.

		Classification by severity	
Stage	Description	GFR mL/min/1.73 m^2	Related terms
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria
3	Moderate ↓ GFR	30–59	Chronic renal insufficiency, early renal insufficiency
4	Severe ↓ GFR	15–29	Chronic renal insufficiency, late renal insufficiency, pre-ESRD
5	Kidney failure	<15 (or dialysis)	Renal failure, uremia, end-stage renal disease

Stage 5 of CKD is also known as End Stage Kidney Disease (ESKD) and patients in this stage require renal replacement therapy in the form of dialysis or receive kidney transplant ***(Levey et al., 2005).***

Residual kidney function (RKF) in ESKD patients on regular hemodialysis (HD) is associated with better prognosis ***(Vilar et al., 2009).*** Nutrition ***(Sudha et al., 2000)***, volume overload and uremic toxins ***(Marquez et al., 2011)***, inflammation and anemia ***(Shafi et al., 2010)*** are all improved with preserved RKF in ESKD. Mortality also decreases with preserved RKF in ESKD ***(Von Der Wal et al., 2011).***

RKF can be expressed as urinary clearance of urea (KRU) ***(Shafi et al., 2016).*** If KRU is ≥2ml/min it can be included in hemodialysis adequacy reducing the frequency of HD sessions required per week ***(Hemodialysis adequacy workgroup, 2006).*** Measuring KRU directly in HD patients usually requires 24 hour urine collection which makes it difficult and more prone to errors ***(Hemodialysis adequacy workgroup, 2006).*** Serum creatinine is used in non HD patients to estimate GFR but is not accurate enough in estimating KRU and RKD in ESKD patients as it is not in steady state and is affected by HD ***(Shafi et al., 2016)***. Therefore, there is a need for serum biomarkers which are accurate, easy to measure and does not need urine collection.

Beta trace protein(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 by the choroid plexus, oligodendrocytes and leptomeninges in central nervous system and also by the retina,kidneys,testes and heart but is exclusively excreted by

the kidneys ***(Olsson et al., 1973).*** Serum BTP is correlated with GFR ***(White et al., 2015).*** Conventional and high flux HD minimally effect the clearance of BTP and hence it will be in steady state in patients receiving HD ***(Gerhardt et al., 2008).*** These features makes BTP a good candidate for estimating KRU and thus RKF.

Dialysis specific equation using serum BTP was recently developed to estimate the KRU and thus RKF in HD patients. This equation was also validated in 826 patients. Bias using this equation in development and validation studies was low and precision and accuracy was significantly high. Sex coefficients was significant in development study suggesting association of BTP and RKF differs by sex. BTP also decreases with corticosteroid use and its use maybe be unreliable in patients using corticosteroids. Thus equations using serum BTP can be used to estimate KRU and RKF more accurately without the need of timed urine collection ***(Shafi et al., 2016).***

AIM OF STUDY

In this study we aim to compare the KRU estimated from the equation using serum pre-dialysis BTP with KRU measured using serum and urinary urea in 2 groups of ESKD patients, Group-1(G-1) those with daily urine output of >500ml to patients and Group-2(G-2) those with daily urine output of 200-500 ml.

Chapter 1

CHRONIC KIDNEY DISEASE

I. Definition

Chronic kidney disease(CKD) definition have evolved over time. Its diagnosis is established by proving the chronic reduction in kidney functions or presence of chronic structural damage. Kidney function can be measured using glomerular filtration rate(GRF) which equals to amount of fluids filtered by the kidneys per unit time ***(Levey et al., 2015).***

Normally an adult person would have a GFR of more than 90ml/min per $1.73m^2$.Current guidelines define CKD as a decrease in GFR of less than 60 ml/min per $1.73m^2$ or presence of markers of kidney damage for at least 3 months. Markers of kidney damage may be abnormal urinary content like albuminuria or abnormal histology or imaging. CKD can develop from a variety of heterogeneous diseases, however diabetes and hypertension are its main causes in many countries ***(Andrassy, 2013).***

II. Classification

CKD has been classified by the Kidney Disease Outcome Quality Initiatives (K/DOQI) into 5 stages according to GFR with the subdivision of stage 3 in G3a (45 to 59 mL/min per 1.73 m^2) and G3b (30 to 44 mL/min per 1.73 m^2). Albuminuria