LABORATORY TEST FOR RESIDUAL RENAL FUNCTION ASSESSMENT IN DIALYSIS PATIENTS

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INTRODUCTION

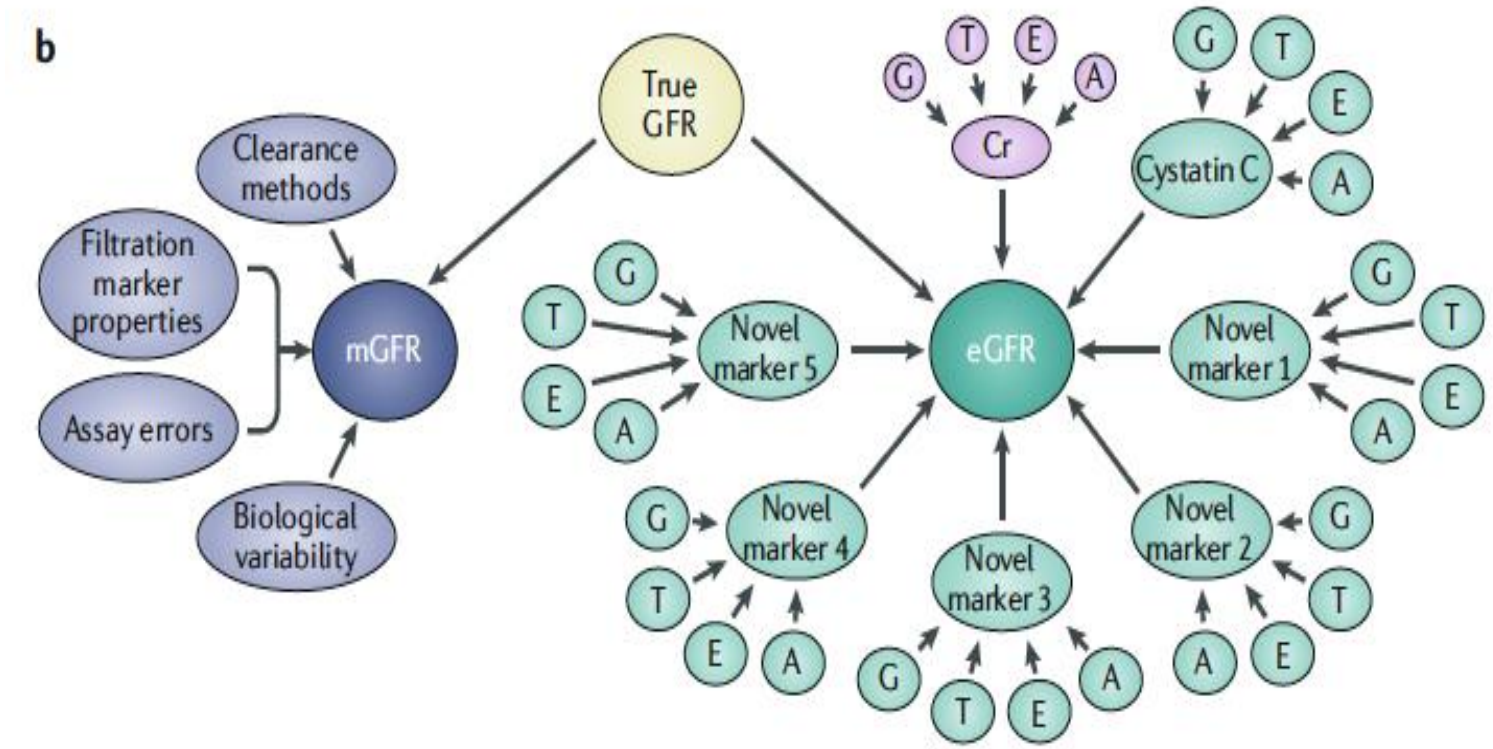
Chronic Kidney Disease: is a gradual loss of kidney function over time. The loss of function may be so slow that the patient has no symptoms until the final stage.

CKD is defined as the presence of kidney damage, or an eGFR < 60 ml/min per 1.73 m^2, persisting for $\geq$ 3 months.

At the final stage (ESRD) the kidney are unable to remove enough wastes and excess fluid from the body → may need kidney replacement therapy : dialysis or a kidney transplant

RENAL FUNCTION

- Renal function: measured by glomerular filtration rate (GFR)
- GFR : measured & estimated



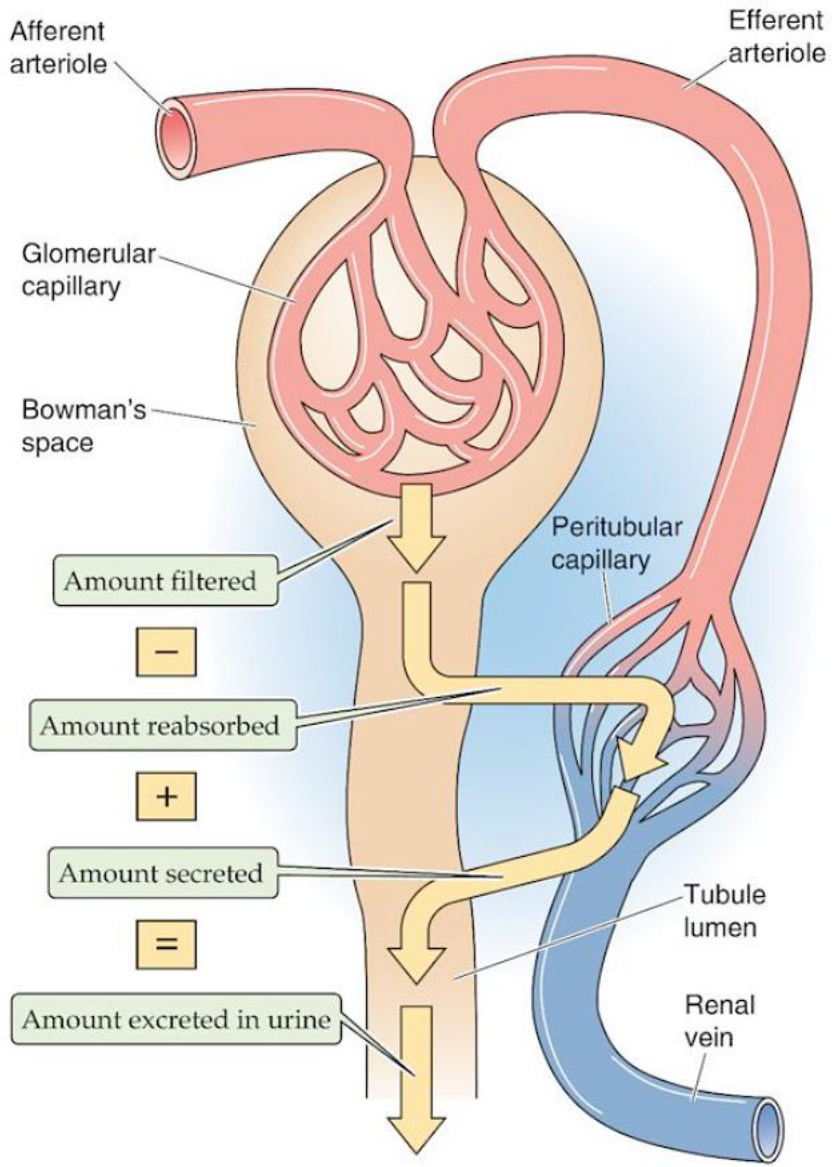
Levey, A.S., Coresh, J., Tighiouart, H. *et al.* Measured and estimated glomerular filtration rate: current status and future directions. *Nat Rev Nephrol* **16**, 51–64 (2020).

CLEARANCE

- Defined as: the volume of plasma cleared of a marker by excretion per unit of time.
- Clearance of substance x is the sum of the urinary and extrarenal clearance. For substances that are eliminated by renal and extrarenal routes, plasma clearance exceeds urinary clearance.
- Urinary clearance: the amount of substance x excreted in the urine can be calculated as the product of the urinary flow rate (V) and urinary concentration of substance x (Ux).

URINARY CLEARANCE

- Urinary excretion of a substance depends on filtration, tubular secretion, and tubular reabsorption.
- Substances that are filtered but not secreted or reabsorbed by the tubules are ideal filtration markers.
- For substances that are filtered + secreted: clearance > GFR
- For substances that are filtered + reabsorbed : clearance < GFR.
- Measurement of urinary clearance requires a timed urine collection for measurement of urine volume, urine and plasma concentration of the marker.
- Weakness: incomplete urine collection may affect the clearance calculation accuracy.



PLASMA CLEARANCE

- Measurement of plasma clearance do not require a timed urine collection.
- GFR is calculated from plasma clearance after a bolus intravenous injection of an exogenous filtration marker.
- Clearance is calculated from the amount of administered marker (Ax) divided by the plasma concentration (Px). Cx – Ax/Px
- Plasma clearance is best estimated by use of a two-compartment model that requires blood sampling early (usually 2-3 x until 60 minutes), and late (1-2 x from 120 minutes onward).
- Weakness: depends on filtration, tubular secretion, tubular reabsorption, and extra-renal elimination.

EXOGENOUS FILTRATION MARKER

Marker	Method of Administration	Comments
Inulin	Continuous IV	Gold standard
Iothalamate	Bolus IV or subcutaneous	Can be administered as radioactive compound with ^{125}I as the tracer or in nonradioactive form, with assay using HPLC methods. In radioactive form, potential problem of thyroid uptake of ^{125}I. Iothalamate is secreted, leading to overestimation of GFR
^{99m}Tc-DTPA	Bolus IV	Dissociation of ^{99m}Tc leads to plasma protein binding and under-estimation of GFR
^{51}Cr-EDTA	Bolus IV	10% lower clearance than inulin
Iohexol	Bolus IV	Low incidence of adverse effects Comparable to inulin Expensive and difficult to perform assay

ENDOGENOUS FILTRATION MARKERS

Comparison of Creatinine, Urea, and Cystatin C as Filtration Markers

Variable	Creatinine	Urea	Cystatin C
Molecular properties			
Weight	113 daltons	60 daltons	13,000 daltons
Structure	Amino acid derivative	Organic molecular product of protein metabolism	Nonglycosylated basic protein
Physiologic determinants of serum level			
Generation	Varies, according to muscle mass and dietary protein; lower in elderly persons, women, and Caucasians	Varies, according to dietary protein intake and catabolism	Thought to be constant by all nucleated cells; variation in cystatin levels, independent of GFR, may be due to generation
Handling by the kidney	Filtered, secreted, and excreted in the urine	Filtered, reabsorbed, and excreted in the urine	Filtered, reabsorbed, and catabolized
Extarenal elimination	Yes; increases at reduced GFR	Yes; increases at reduced GFR	Preliminary evidence of increases at reduced GFR
Use in estimating equations for GFR			
Demographic and clinical variables as surrogates for physiologic determinants	Age, sex, and race; related to muscle mass	Not applicable	Unknown
Accuracy	Accurate for GFR <60 ml/min/1.73 m^2	Not applicable	Unknown
Assay			
Method	Colorimetric or enzymatic	Direct measurement, enzymatic, colorimetric, and electrochemical	PENIA or PETIA
Assay precision	Very good except at low range	Precise throughout the range	Precise throughout the range
Clinical laboratory practice	Multiple assays; widely used nonstandard calibration	Multiple assays; enzymatic and colorimetric more commonly used	Not on most autoanalyzers; not standardized
Reference standard	IDMS	IDMS	None at present

GFR, glomerular filtration rate; IDMS, isotope dilution gas chromatography–mass spectroscopy; PENIA, particle-enhanced nephelometric immunoassay; PETIA, particle-enhanced turbidimetric immunoassay.

CREATININE

- An end product of muscle catabolism.
- Derived by the metabolism of phosphocreatine in muscle, dietary meat intake or creatine supplements
- Released into the circulation at a constant rate.
- It is not protein bound and is freely filtered across the glomerulus and secreted by the tubules.
- Affected by several factors
- Contained in intestinal secretion and can be degraded by bacteria.
- At normal levels of GFR, tubular levels are relatively small (10-15%)
- But: at low values of GFR, the amount of creatinine excreted by tubular secretion may exceed the amount of filtered

Factors Affecting Serum Creatinine Concentration

	Effect on Serum Creatinine	Mechanism/Comment
Age	Decrease	Reduced creatinine generation due to age-related decline in muscle mass
Female sex	Decrease	Reduced creatinine generation due to reduced muscle mass
Race		
African American	Increase	Higher creatinine generation due to higher average muscle mass in African Americans; not known how muscle mass in other races compares with that of African Americans or Caucasians
Diet		
Vegetarian diet	Decrease	Decrease in creatinine generation
Ingestion of cooked meats and creatinine supplements	Increase	Transient increase in creatinine generation; however, this may be blunted by transient increase in GFR

	Effect on Serum Creatinine	Mechanism/Comment
Body habitus		
Muscular	Increase	Increased muscle generation due to increased muscle mass ± increased protein intake
Malnutrition, muscle wasting, amputation	Decrease	Reduced creatinine generation due to reduced muscle mass ± reduced protein intake
Obesity	No change	Excess mass is fat, not muscle mass, and does not contribute to increased creatinine generation
Medications		
Trimethoprim, cimetidine, fibric acid derivatives other than gemfibrozil	Increase	Reduced tubular secretion of creatinine
Keto acids, some cephalosporins	Increase	Interference with alkaline picrate assay for creatinine

RESIDUAL RENAL FUNCTION

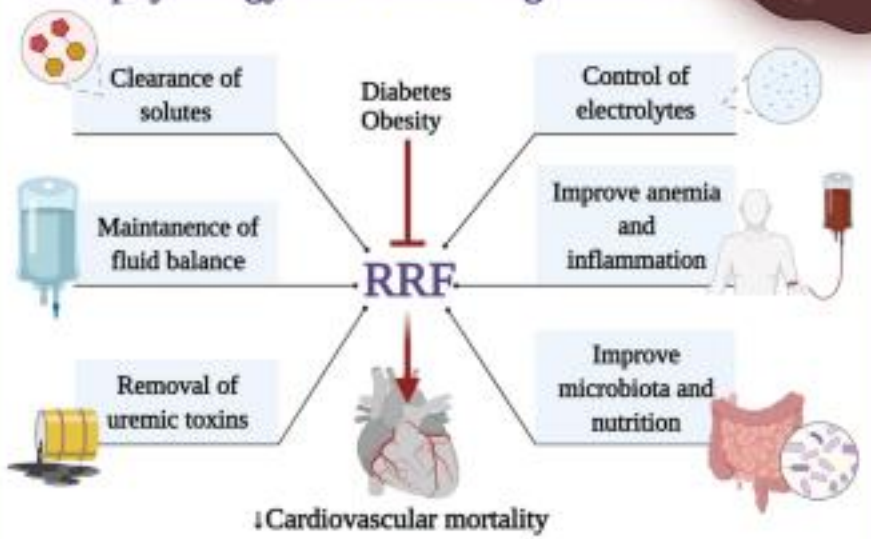
- Most patient ESRD excrete 100-250 ml of urine daily for months after hemodialysis or peritoneal dialysis begun.
- defined as the ability of the native kidneys to eliminate water and uremic toxins
- Is quantified as “clearance” by measurement of urea, creatinine, or urea and creatinine clearance in urine voided in the interval between dialysis session.
- RRF is a powerful prognostic indicator, and preservation of RRF is associated with better survival, lower morbidity, and greater quality of life in patients with ESRD on PD or HD

Residual Renal Function

Background

- Chronic kidney disease is on the rise leading to an increase in hemodialysis (HD) and peritoneal dialysis (PD) patients.
- Residual renal function (RRF) decreases morbidity and mortality in HD and PD patients.

Pathophysiology and Clinical Significance



Preservation of RRF

Prevent RRF decline;

- Renin-angiotensin-aldosterone system blockage
- Blood pressure management
- Diuretic treatment
- Incremental PD
- Icodextrin solution
- Incremental HD
- Biocompatible HD membrane

Current Trials and Future Directions

As of February 2022, there are 28 listed trials on RRF. The completion of the ongoing trials as well as future studies are required to broaden our understanding of the pathophysiology and preservation of RRF.

Tanriover, C. *et al.* On the importance of the interplay of residual renal function with clinical outcomes in end-stage kidney disease. *J Nephrol* **35**, 2191–2204 (2022).

MEASUREMENT OF RESIDUAL RENAL FUNCTION

- RRF may be estimated and measured.
- However, an optimal method for measuring RRF has not been established.
- The glomerular filtration rate (GFR) is widely used as an indicator for kidney function.
- Formulas based on the serum creatinine level are clinically used to estimate the GFR before initiation of renal replacement therapy.
  - The Schwartz formula and the Counahan-Barratt equation are used in children.
  - The Modification of Diet in Renal Disease (MDRD) equation and the Cockcroft-Gault formula are used in adults.

MEASUREMENT OF RESIDUAL RENAL FUNCTION

- The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines:
  - measuring RRF by calculating the mean 24-hour urine creatinine level and urea clearance scaled on a patient's body surface area and expressed as ml/min/1.73 m2 or l/week/1.73 m2 for both PD and HD patients.
  - The time of collecting 24-hour urine is crucial; from PD patients who are in stable condition, 24-hour urine can be collected on a random day, but from HD patients, some clinicians advocate collecting urine in the entire interdialytic interval because of these patients' hemodynamic instability

PROBLEMS

- Since accurately quantifying RRF from urine is arduous, there is a clinical need to develop alternative methods of assessing RRF based on serum testing
- due to the elimination by dialysis.

BETA TRACE PROTEIN

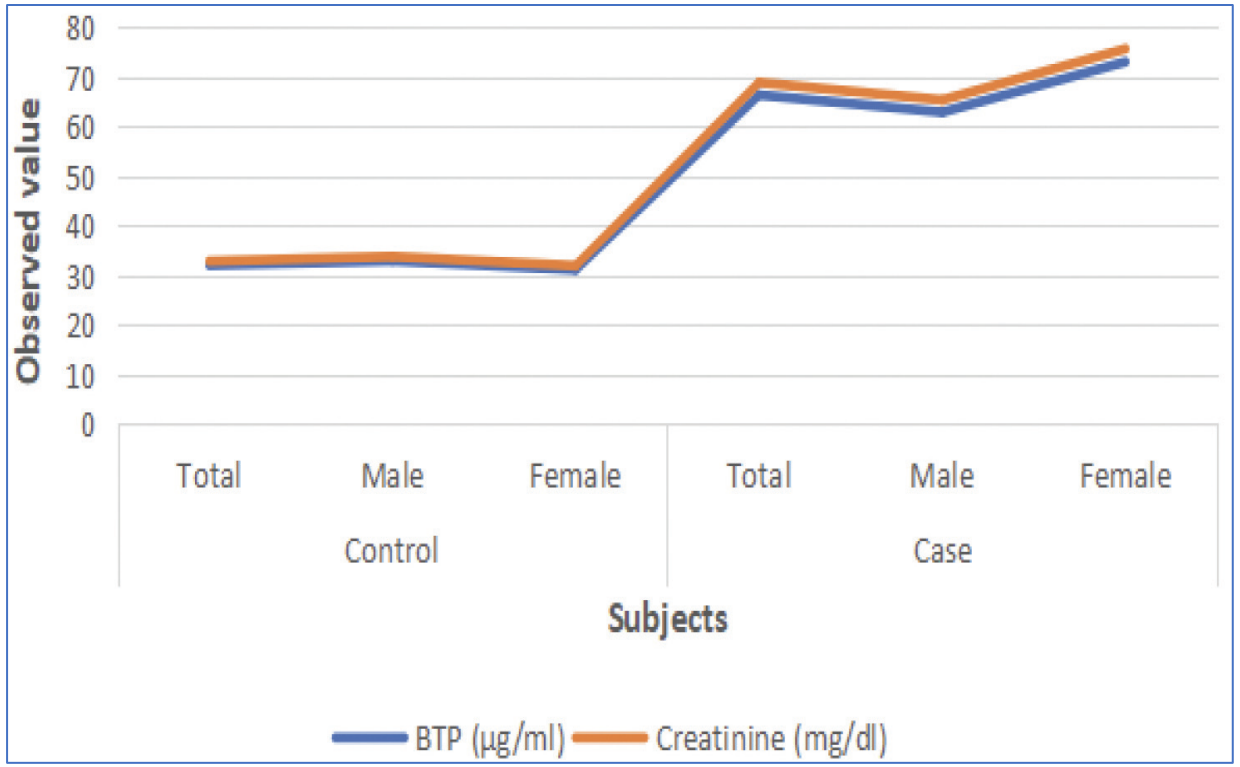
- also known as prostaglandin D2 synthase
- a low-molecular-weight glycoprotein (25.2kDa)
- initially isolated from cerebrospinal fluid and served as a marker of cerebrospinal fluid leakage .
- It is expressed in almost all tissues, with biological actions that include vasodilatation, bronchoconstriction, inhibition of platelet aggregation, and recruitment of inflammatory cells.
- The half-life of BTP is approximately 1.2 h
- it is freely filtered through the glomerular basement membrane with minimal nonrenal elimination

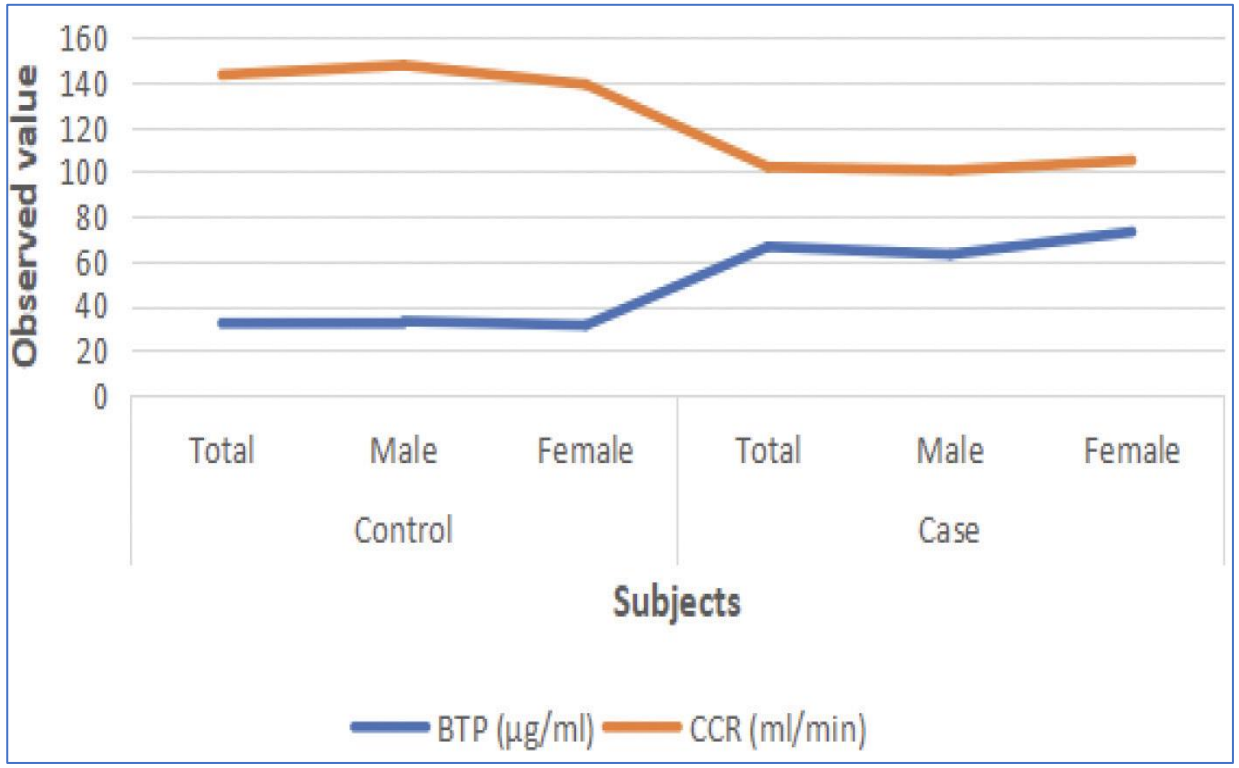
Serum concentrations of BTP and Cys-C.

Variables	Groups (Mean ± SD)			*P*- value
	Control	Renal impairment (Pre-dialysis)	Undergoing hemodialysis	
BTP (pg/ml)	480 ± 40	752 ± 140	2903 ± 3173	0.001
Cys-C (ng/ml)	72 ±14	312 ± 187	1486 ± 1066	
Note: Cys-C = Cystatin C; BTP = beta trace protein				

El-Aarag B, Abdu-Allah AM, Abo-Alfa MA, El Sayed IT (2018) Serum Beta-trace Protein and Cystatin C as Biomarkers for Renal Dysfunction in Patients with Chronic Kidney Disease. J Mol Biomark Diagn 9: 399. doi: 10.4172/2155-9929.1000399

BTP in CHRONIC KIDNEY DISEASE





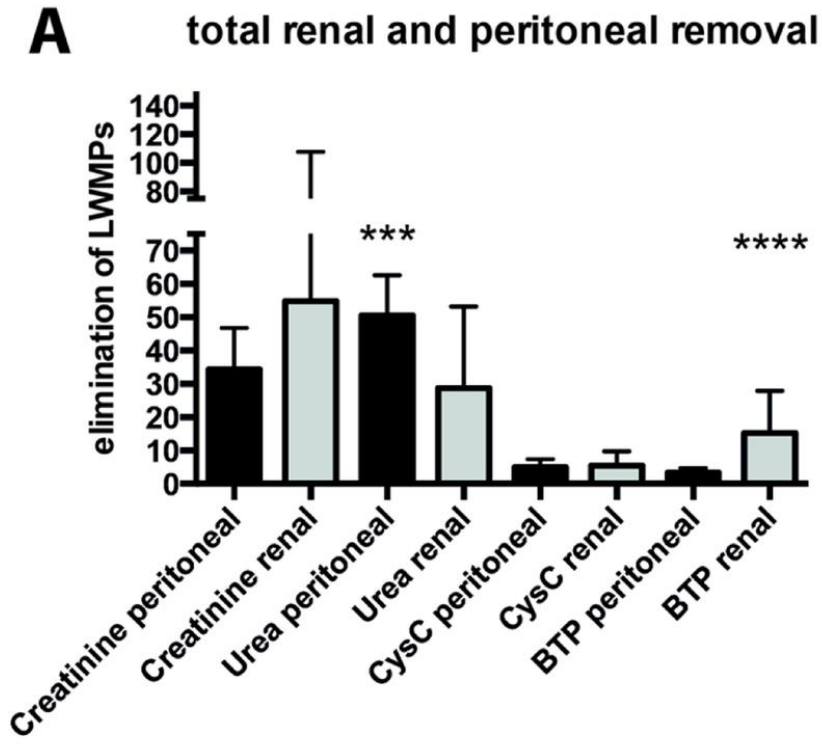
Journal of Clinical and Diagnostic Research. 2022 Dec, Vol-16(12): BC15-BC18

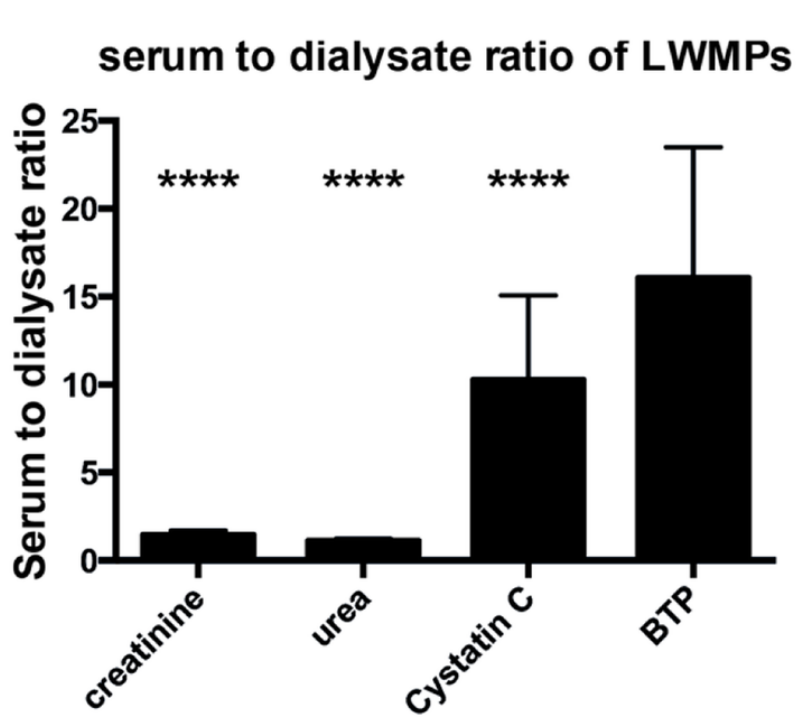
The correlations of BTP and Cys-C levels with urea, creatinine, and eGFR

Variables	BTP		Cys-C	
	Renal impairment (Pre-dialysis)	Renal Impairment & Hemodialysis	Renal impairment (Pre-dialysis)	Renal Impairment & Hemodialysis
Urea	0.801**	0.549**	0.706**	0.697**
Creatinine	0.973**	0.772**	0.908**	0.906**
eGFR	- 0.8**	- 0.364**	- 0.655**	- 0.52**
Note: *r*: Pearson correlation; + *r*: Positive correlation (direct); - *r*: Negative correlation (inverse); **: $P<0.01$				

El-Aarag B, Abdu-Allah AM, Abo-Alfa MA, El Sayed IT (2018) Serum Beta-trace Protein and Cystatin C as Biomarkers for Renal Dysfunction in Patients with Chronic Kidney Disease. J Mol Biomark Diagn 9: 399. doi: 10.4172/2155-9929.1000399

BTP IN PERITONEAL DIALYSIS





Schwab, S. *et al.*. *BMC Nephrol* **22**, 87 (2021).

SUMMARY

- Chronic kidney disease is a condition of gradual loss of renal function that may lead to end stage renal disease requires renal replacement therapy.
- GFR is one parameter represents renal function.
- GFR is measured by clearance of exogenous or endogenous substance
- Creatinine is currently the most used marker to determine GFR. However, it's serum concentration is affected by several factors.
- Residual renal function is important for dialysis patients, as it is a strong indicator for prognosis, and correlate with lower morbidity and mortality, and better quality of life.
- Ureum and creatinine are currently used to determine RRF. However, they are removed by dialysis and affected by non-renal factors.
- Beta trace protein potentially be a better marker for RRF of dialysis patients as it is not removed by dialysis process and minimally affect by non-renal factors.