Review Article **OPEN ACCESS**

Markers of renal function tests

Shivaraj Gowda, Prakash B. Desai, Shruthi S. Kulkarni, Vinayak V. Hull, Avinash A. K. Math, Sonal N. Vernekar.

Department of Biochemistry, Jawaharlal Nehru Medical College, Belgaum 590010, Karnataka, India.

Citation: Gowda S, Desai PB, Kulkarni SS, Hull VV, Math AAK, Vernekar SN. Markers of renal function tests. **North Am J Med Sci** 2010; 2: 170-173.
Availability: www.najms.org
ISSN: 1947 – 2714

Abstract

Background: The markers of renal function test assess the normal functioning of kidneys. These markers may be radioactive and non radioactive. They indicate the glomerular filtration rate, concentrating and diluting capacity of kidneys (tubular function). If there is an increase or decrease in the valves of these markers it indicates dysfunction of kidney. **Aim:** The aim of this review is to compare and analyze the present and newer markers of renal function tests which help in diagnosis of clinical disorders. **Material & Methods:** An extensive literature survey was done aiming to compare and compile renal function tests makers required in diagnosis of diseases. **Results:** Creatinine, urea, uric acid and electrolytes are makers for routine analysis whereas several studies have confirmed and consolidated the usefulness of markers such as cystatin C and β-Trace Protein. **Conclusion:** We conclude that further investigation is necessary to define these biomarkers in terms of usefulness in assessing renal function.

Keywords: Creatinine, creatinine clearance, urea, cystatin C, β-trace protein, inulin, iohexol, electrolyte.

Correspondence to: Dr Shivaraj Gowda, Associate Professor, Department of Biochemistry, J.N. Medical College, Belgaum 590010. Karnataka. India. Email: drshivaraj@yahoo.com

Introduction

Biochemical markers play an important role in accurate diagnosis and also for assessing risk and adopting therapy that improves clinical outcome. Over decades research and utilization of biomarkers has evolved substantially. National Institute of Health (NIH) 2001 defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological, pathologic processes, or pharmacologic responses to a therapeutic intervention [1]. As markers of renal function creatinine, urea, uric acid and electrolytes are for routine analysis whereas several studies have confirmed and consolidated the usefulness of markers such as cystatin C, β-Trace Protein.

Creatinine

Creatinine is a breakdown product of creatine phosphate in muscle, and is usually produced at a fairly constant rate by the body depending on muscle mass [2]. Creatinine is a commonly used as measure of kidney function.The normal creatinine clearence test valve is 110-150ml/min in male and in female it is 100-130ml/min [3].The National Kidney Disease Education Program recommends calculating glomerular filtration rate from serum creatinine concentration [4]. The creatinine clearance test is used to monitor the progression of renal disease. The diagnosis of renal failure is usually suspected when serum creatinine is greater than the upper limit of the "normal" interval. In chronic renal failure and uremia, an eventual reduction occurs in the excretion of creatinine by both the glomeruli and the tubules [5]. Creatinine values may alter as its generation may not be simply a product of muscle mass but influenced by muscle function, muscle composition, activity, diet and health status [6]. The increased tubular secretion of creatinine in some patients with kidney dysfunction could give false negative value [7]. The elevated values are also seen in muscular dystrophy paralysis, anemia, leukemia and hyperthyroidism. The decreased values are noticed with glomerulonephritis, congestive heart failure, acute tubular necrosis, shock, polycystic kidney disease, and dehydration [5].

Urea

Urea is major nitrogenous end product of protein and amino acid catabolism, produced by liver and distributed throughout intracellular and extracellular fluid. In

kidneys urea is filtered out of blood by glomerulli and is partially being reabsorbed with water [3]. The most frequently determined clinical indices for estimating renal function depends upon concentration of urea in the serum. It is useful in differential diagnosis of acute renal failure and pre renal condition where blood urea nitrogen–creatinine ratio is increased [8]. Urea clearance is a poor indicator of glomerular filtration rate as its overproduction rate depends on several non renal factors, including diet and urea cycle enzymes. Increased blood urea nitrogen (BUN) is seen associated with kidney disease or failure, blockage of the urinary tract by a kidney stone, congestive heart failure, dehydration, fever, shock and bleeding in the digestive tract. The high BUN levels can sometimes occur during late pregnancy or result from eating large amounts of protein-rich foods. If the BUN level is higher than 100 mg/dL it points to severe kidney damage whereas decreased BUN is observed in fluid excess. Low levels are also seen in trauma, surgery, opioids, malnutrition, and anabolic steroid use [9].

Cystatin C

The protease inhibitor Cystatin C is a non-glycosylated low molecular weight protein. Cystatin C has been proposed to be a marker as it is produced by all nucleated cells at a constant rate and is freely filtrated by the glomeruli and completely catabolized in the proximal tubules. The concentration of serum Cystatin C is mainly determined by glomerular filtration, which makes Cystatin C an endogenous marker of glomerular filtration rate [10]. In a Meta analysis study by Dharnidharka et al [11] found Cystatin C was superior to serum creatinine as a marker of glomerular filtration rate. Other studies have shown similar results when compared with other markers such as α 1-microglobulin and β 2-microglobulin [12]. Cystatin C was found to be an effective marker for glomerular filtration rate in patients with cirrhosis following liver transplantation [13, 14]. Cystatin C has been found more useful for detecting early renal impairment in both type 1 and type 2 diabetic patients [15]. Moreover Cystatin C was also found to be associated with mild kidney dysfunction with increased risk for cardiovascular events, peripheral arterial disease and heart failure [16].

β -Trace Protein (BTP)

This protein is filtered at glomerulus and then reabsorbed in proximal tubule or excreted in urine and hence have potential to meet the criteria for use as a marker of glomerular filtration rate [5]. β-Trace Protein is a low-molecular weight glycoprotein belonging to the lipocalin protein family with 168 amino acids and a molecular weight of 23000–29000, depending on the degree of glycosylation. It has been reported to be a better indicator of reduced glomerular filtration rate than serum creatinine [17, 18]. Serum β -Trace Protein has been found to be elevated in patients with renal diseases [19]. However, when compared, Cystatin C is still a better indicator than Serum β-Trace Protein [20].

Inulin

Fructose polymer inulin (MW 5kDa) satisfies the criteria as an ideal marker of glomerular filtration rate. Rapid measurement of glomerular filtration rate by an inulin single-bolus technique would be practically useful [21].

Iohexol

A new technique of measuring iohexol clearance using timed dried capillary blood spots was shown by Mafham M et al [22]. Blood spot iohexol clearance showed potential in estimating glomerular filtration rate accurately in large-scale epidemiological studies especially among individuals without established chronic kidney disease [22]. Plasma clearance after single injection of iohexol gives a good estimate of glomerular filtration rate and is advantageous for the patients and clinicians. Iohexol clearance is also used to estimate residual renal function in hemodialysis patients [23].

Radioactive Markers

In recent decade radioisotopes markers have been used to measure glomerular filtration rate. Some of them to mention are 125iodine (I)-iothalamate, 51CrEDTA ethylenediamine tetra acetic acid, 99mTc-DTPA (diethylene triamine penta acetic acid) and 99mTc mercapto acetyl triglycine. Renal 125iodine (I)-iothalamate clearance, is a simple and accurate test after a single subcutaneous injection, to measure glomerular filtration rate in adults [24]. Efficiency of 125 iodine (I)-iothalamate was shown by Geeta Bajaj et al. The same author found renal clearance of 125 iodine (I)-iothalamate was reproducible, simple, and practical in healthy children and those with mild and advanced renal disease. In one of the study the mean renal extraction of Cystatin C was equal to the mean renal extraction of 125 iodine (I)-iothalamate in hypertensive patients, suggesting tubular secretion of Cystatin C [25]. It was possible to get an accurate determination of 5lCr-EDTA clearance from a single-plasma sample in adults by applying the mean sojourn time-based approach previously shown to be very precise for determination of 99mTc-DTPA single-sample clearance [26]. 5lCr EDTA- glomerular filtration rate is suggested for systemic lupus erythematosus patient with suspected renal involvement even when the serum creatinine concentration and creatinine clearance are normal [27]. The limitation of this marker is that glomerular filtration rate measured by 5lCr EDTA can be overestimated in patients with severe oedema [26].

Proteinuria

Clinically the appearance of significant amount of protein in urine is one of the earliest sign of almost all renal diseases. Estimation of proteinuria helps in differentiating between tubulointerstitial and glomerular diseases and also to follow the progress of renal disease and to assess the response to therapy. Normally excretion in most healthy adults is between 20-150 mg of protein in urine over 24 hrs. Proteinuria more than 3.5 gm/day is taken to be diagnostic of nephrotic syndrome. Panels of protein measurement including albumin, α 2-macroglobulin, IgG

and α 2- microglobulin have been employed in differential diagnosis of prerenal and postrenal disease. It has been recommended the use of the protein/creatinine ratio as an Index of Quantitative Proteinuria in 24 hour urine collection [28]. The prevalence of kidney diseases in people with diabetes was found to have proteinuria [29]. The use of the clearance of haptoglobin, in particular provided valuable diagnostic information in cases in which the routine methods gave borderline values for the index of proteinuria [30]. During pregnancy proteinuria assay in 24 hour urine sample is performed. One of the investigations for proteinuria is semi-quantitative dipstick urinalysis as this method is relatively low cost and easily performed [31].In pregnancy automated dipstick urinalysis is a more accurate screening test for the detection of proteinuria than visual testing. The finding of dipstick proteinuria should be confirmed by either a 24 hour urine collection or a protein-creatinine ratio [32].

Markers of tubular function

Tubular function tests involve evaluation of functions of the proximal tubule (i.e. tubular handling of sodium, glucose, phosphate, calcium, bicarbonate and amino acids) and distal tubule (urinary acidification and concentration) [33]. Tsukahara H et al [34] assessed the renal proximal tubular function in neonates by measuring urinary β 2-microglobulin concentrations. Chen JY et al [35] showed that in sick neonates the urinary β 2-microglobulin and N-acetyl-β-D-glucosaminidase were the early markers of renal tubular dysfunction. They concluded that the elevated levels of urinary β 2-microglobulin and N-acetyl-β-D-glucosaminidase in neonates born with meconium-stained amniotic fluid indicated the existence of tubular dysfunction, probably due to prenatal distress.

Concentration and Dilution methods

Serum osmolality was measured directly using osmometry, or estimated based on the direct measurement of the concentrations of the osmotically active substances (i.e. sodium, glucose, blood urea nitrogen, and ethanol). The difference between the measured osmolality and the calculated molarity is referred to as the osmole gap [36]. Laloë PA et al [37] observed severe hyponatraemia in some of the patients by measuring urine osmolality and urine sodium. According to Jeff MS [38] there are some genes which are involved in urine concentration which may encode solute-transport proteins and the vasopressin receptors. These molecular mechanisms show the reduction in urine-concentrating ability with aging that predicts various changes in kidney function. While Landon S et al [39] showed that aquaporin-1 has a physiologic role in renal function and is also essential for maximal urinary concentrating ability. In a complete deficiency of Aquaporin-1 there is defective urine concentrating ability.

Electrolyte

Electrolyte panel is frequently used to screen for an electrolyte or acid-base imbalance and to monitor the effect of treatment on a known imbalance that is affecting bodily organ function. The test for electrolytes includes the measurement of sodium, potassium, chloride, and bicarbonate for both diagnosis and management of renal, endocrine, acid-base, water balance, and many other conditions. Potassium used as a most convincing electrolyte marker of renal failure. The combination of decreased filtration and decreased secretion of potassium in distal tubule during renal failure cause increased plasma potassium. Hyperkalemia is the most significant and life-threatening complication of renal failure [40].

Conclusion

The above discussed glomerular and tubular function markers are effective in proper assessment of renal function tests. These markers act as an indicator of biological, pathologic processes, or pharmacologic responses to a therapeutic intervention.

References

1. Ramachandran SV. Biomarkers of Cardiovascular Disease Molecular Basis and Practical Considerations. Circulation 2006; 113: 2335-2362.
2. Yuegang Z, Chengjun W et al. Simultaneous Determination of Creatinine and Uric Acid in Human Urine by High Performance Liquid Chromatography. Anal Sci 2008; 24: 1589-1592.
3. Corbett JV. Laboratory tests and diagnostic procedures with nursing diagnoses. 7th Ed. 2008; 90-107.
4. Miller W, Myers G, Ashwood E et al. Creatinine measurement: state of the art in accuracy and interlaboratory harmonization. Arch Pathol Lab Med 2005; 129(3): 297-304.
5. Edmund L, David J. Kidney function tests. In: Carl AB, Edward R, David E .eds. Tietz Textbook of clinical chemistry and molecular diagnostics. 4th ed. New Delhi: Elsevier Inc; 2006: 797-808.
6. Banfi G, Del F. Serum creatinine values in elite athletes competing in 8 different sports: comparison with sedentary people. Clin Chem 2006; 52: 330–331.
7. Branten AJ, Vervoort G, Wetzels JF. Serum creatinine is a poor marker of GFR in nephrotic syndrome. Nephrol Dial Transplant 2005; 20: 707–711.
8. Mitchell HR and Kline W. Core curriculum in nephrology, Renal Function Testing. Am J Kidney Dis 2006; 47: 174-183.
9. Pagana, Kathleen D. Mosby's Manual of Diagnostic and Laboratory Tests. St. Louis Mosby, Inc., 1998 and Rebecca J.F Gale Encyclopedia of Medicine. 2002.
10. Randers E, Erlandsen EJ. Serum Cystanin C as an endogenous marker of the renal function a review. Clin Chem Lab Med 1999; 37(4): 389-395.
11. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. Am J Kidney Dis 2002; 40: 221–226.
12. Guido F, Friedrich P, Nathalie L et al. ß-Trace Protein,

Cystatin C, ß2-Microglobulin, and Creatinine Compared for Detecting Impaired Glomerular Filtration Rates in Children. Clin Chem 2002; 48: 729-736.
13. Cholongitas E, Shusang V, Marelli L et al. Review article: renal function assessment in cirrhosis - difficulties and alternative measurements. Aliment Pharmacol Ther 2007; 26(7): 969-978.
14. Gerbes AL, Gulberg V, Bilzer M et al. Evaluation of serum cystatin C concentration as a marker of renal function in patients with cirrhosis of the liver. Gut 2002; 50: 106–110.
15. Laura P, Stefano T, Daniela L et al. Cystatin C and Estimates of Renal Function: Searching for a Better Measure of Kidney Function in Diabetic Patients. Clin Chem 2007; 53: 480-488.
16. Shlipak MG, Katz R, Fried LF et al. Cystatin-C and mortality in elderly persons with heart failure. J Am Coll Cardiol 2005; 45:268-271.
17. Priem F, Althaus H, Birnbaum M, et al. ß-trace protein in serum: a new marker of glomerular filtration rate in the creatinine-blind range. Clin Chem 1999; 45: 567-568.
18. Woitas RP, Stoffel-Wagner B, Poege U et al. Low-molecular weight proteins as markers for glomerular filtration rate. Clin Chem 2001; 47: 2179-2180.
19. Hoffmann A, Nimtz M, Conradt H. Molecular characterization of ß-trace protein in human serum and urine: a potential diagnostic marker for renal diseases. Glycobiology 1997; 7: 499-506.
20. Priem F, Althaus H, Jung K, Sinha P. ß-Trace protein is not better than cystatin C as an indicator of reduced glomerular filtration rate. Clin Chem 2001; 47: 2181.
21. Jacobsen LA. Method for calculation of renal clearance based upon a single plasma sample. Clin Physiol 1983; 3: 297-305.
22. Mafham MM, Niculescu-Duvaz I, Barron J, et al. A practical method of measuring glomerular filtration rate by iohexol clearance using dried capillary blood spots. Nephron Clin Pract 2007; 106(3):104-112.
23. Swan Sk, Nalstenson CE, Kasiske BL et al. Determination of residual renal function with iohexol clearance in hemodialysis patients. Kidney Int 1996; 49:232-235.
24. Geeta B, Steven R, Richard B et al. 125Iodine-iothalamate clearance in children. A simple method to measure glomerular filtration. J Pediatr Nephrol 1996; 10: 25-28.
25. Lyonne K, Robert Z, Arnold G, Yolanda B. Renal extraction of cystatin C vs. 125I-iothalamate in hypertensive patients. Nephrol Dial Transplant 2006; 21(5): 1253-1256.
26. Johan M, Steffen G, Michael R, Margareta G. Chromium-51-EDTA Clearance in Adults with a Single-Plasma Sample. J Nucl Med 1998; 39:2131-2137.
27. Godfrey T, Cuadrado MJ, Fofi C et al. Chromium-51 ethylenediamine tetraacetic acid glomerular filtration rate: a better predictor than glomerular filtration rate calculated by the Cockcroft–Gault formula for renal involvement in systemic lupus erythematosus patients. Rheumatology 2001; 40: 324-328.
28. Sandeep G, Alok Kumar G, Anurag R et al. Evaluation of Random Urine Sample Protein-Cretinine Ratio as an Index of Quantitative Proteinuria. JK science 2004; 6:134-137.
29. Jerums G and MacIsaac RJ. Treatment of microalbuminuria in patients with type 2 diabetes mellitus. Treat Endocrinol 2002; 1(3):163-173.
30. Tishkov, Razboynikov S, Tchoukanov C et al. Biochemical methods for the assessment of the selectivity of proteinuria. J Int Urol Nephrol: 1978; 10: 245-249.
31. Helena M and Jason W. Proteinuria in pregnancy – just what is significant? J Matern Fetal Med 2004; 16:171–195.
32. Jason JS, Stephen CB, Mark DK et al. Optimal bedside urinalysis for the detection of proteinuria in hypertensive pregnancy: a study of diagnostic accuracy. BJOG 2005; 112: 412 – 417.
33. Arvind B, Anurag B and Shina M. Approach to Renal Tubular Disorders. Indian J Pediatr 2005; 72 (9): 771-776.
34. Tsukahara H, Yoshimoto M, Saito M et al. Assessment of tubular function in neonates using urinary beta 2-microglobulin. Pediatr Nephrol 1990; 4(5): 512-514.
35. Chen JY, Lee YL and Liu CB.Urinary beta 2-microglobulin and N-acetyl-beta-D-glucosaminidase (NAG) as early markers of renal tubular dysfunction in sick neonates. J Formos Med Assoc 1991; 90(2):132-137.
36. Purssell RA, Lynd LD, and Koga Y. The osmole gap as a screening test for the presence of toxic substances: a review of the literature. Toxicol Rev 2004; 23(3):189-202.
37. Laloë P.A, Wong A and Murphy MJ. Results of measurement of urine osmolality and sodium in the evaluation of severe hyponatraemia. Clin Pathol 2003; 56(11): 883–884.
38. Jeff MS. Urine-Concentrating Ability in the Aging Kidney. Sci. Aging Knowl Environ 2003; 24: 15.
39. Landon S, Michael C, Pedro C. Defective Urinary Concentrating Ability Due to Complete Deficiency of Aquaporin-1. NEJM 2001; 345:175-179.
40. James S, Mitchel G .physiology and disorder of water electrolytes and acid base metabolism. In: Carl AB, Edward R, David E .eds. Tietz Textbook of clinical chemistry and molecular diagnostics. 4th ed. New Delhi, Elsevier Inc 2006: 1747-1776.