

Markers of renal function tests

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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 values 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.

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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 clearance test value 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 glomeruli 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, ^{99m}Tc-DTPA (diethylene triamine penta acetic acid) and ^{99m}Tc 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 ¹²⁵iodine (I)-iothalamate was shown by Geeta Bajaj et al. The same author found renal clearance of ¹²⁵iodine (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 ¹²⁵iodine (I)-iothalamate in hypertensive patients, suggesting tubular secretion of Cystatin C [25]. It was possible to get an accurate determination of ⁵¹Cr-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 ^{99m}Tc-DTPA single-sample clearance [26]. ⁵¹Cr 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 ⁵¹Cr 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 $\alpha 2$ -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.

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