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Review article

Assessment of Renal Functions in Patients with Liver Disease: Which One is Correct?

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Abstract

Renal dysfunction is a major complication in patients with liver disease and it is associated with poor prognosis. The accurate evaluation of renal function by Glomerular Filtration Rate (GFR) is important to establish the onset, severity and progression of renal disease and it is required for proper drug dosing, staging of chronic kidney disease (CKD) and determining candidates for combined liver-kidney transplantation. Serum creatinine and creatinine-based equations are the most widely used indirect measures of GFR. But, due to a number of reasons, they do not reflect the degree of renal dysfunction and must be interpreted with caution. Accurate measurement of GFR requires use of a validated filtration marker, such as iothalamate, iohexol, or inulin. Recent filtration markers for estimating GFR, such as cystatin C, should be tested for population of patients with liver diseases.
This article reviews markers of renal function and their potential use in patients with chronic liver disease and cirrhosis.

Keywords: chronic liver disease, cirrhosis, renal dysfunction, Glomerular Filtration Rate (GFR)

Introduction

Chronic liver disease and cirrhosis are frequently complicated with renal dysfunction and this combination leads to significant morbidity and mortality. There is substantial evidence that renal failure in cirrhotic patients is related to the disturbance in circulatory function due to reduction in systemic vascular resistance, and may be secondary to the primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension [1]. Patients with cirrhosis who have circulatory dysfunction and arterial hypoperfusion are particularly prone to acute renal failure (ARF), which may occur spontaneously or may be triggered by a number of events that occur frequently in cirrhosis. Hypovolemia induced by renal (e.g. excessive administration of diuretics) or gastrointestinal (e.g. bleeding, diarrhea) fluid losses, bacterial infections (most often gram-negative peritonitis) and administration of nephrotoxic drugs (e.g. amino glycoside antibiotics, nonsteroidal anti-inflammatory drugs) is a common cause of renal dysfunction in cirrhotic patients [2-5]. Intrinsic renal diseases may occur in patients with hepatitis B or hepatitis C and alcoholic cirrhosis [6]. Moreover, patients with cirrhosis may develop a specific acute renal failure called type 1 hepatorenal syndrome (HRS) [7,8]. Independent of events that lead to ARF, patients with cirrhosis may have diseases, such as diabetes mellitus or hypertension and atherosclerosis, which may cause chronic renal injury [9,10]. Finally, cyclosporine nephrotoxicity may occur in patients with liver transplantation and may cause renal failure that progress to end-stage renal disease (ESRD) [11].

Why should renal functions be determined?

The accurate evaluation of renal functions by Glomerular Filtration Rate (GFR) is important to establish the onset, severity and progression of renal disease. Furthermore, the correct assessment of GFR in patients with liver disease is required for exact drug dosing, staging of chronic kidney disease (CKD) and determining candidates for combined liver-kidney transplantation. Finally, the prognostic value of renal function is emphasized by the inclusion of serum creatinine (Cr) in the Model for End-Stage Liver Disease (MELD) score, which includes the international normalized ratio (INR), serum Cr and serum billirubin [12]. The MELD score was validated as an accurate predictor of survival among different populations of patients with advanced liver disease [13]. However, the major use of MELD score is in allocation of organs for liver transplantation [14]. According to the importance of prognostic value of renal dysfunction, the accurate assessment of renal functions in patients with liver disease is becoming crucial and necessary.

Assessment of Renal Functions

GFR is the test that best detects abnormalities in renal function and it is traditionally measured by renal clearance of a particular substance or marker from the plasma.

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İnulin satisfies the criteria for an ideal clearance substance since it is freely filtered at the glomerulus and is not reabsorbed, secreted, synthesized or metabolized by the tubules. Hence, renal clearance of inulin is the gold standard for GFR measurement [15]. But due to difficulty of administration and cost, its use in routine clinical practice is limited. Plasma creatinine level and endogenous creatinine clearance (Ccr) are commonly used as more convenient but less accurate methods of GFR assessment.

Interpretation of renal function indicators in patients with liver diseases

Serum Creatinine

Creatinine is a metabolic product of creatine and phosphocreatine, which are both synthesized in liver and stored in muscle cell. Therefore, creatinine production is proportional to muscle mass and varies little from day to day [16]. Age and gender-associated differences in creatinine production are related with differences in muscle mass. Creatinine is freely filtered by the glomerulus and is also secreted by renal tubules. Thus, serum creatinine concentration is determined by production, storage and renal elimination together.

Patients with liver disease have several underlying conditions that contribute to falsely low serum creatinine concentrations, besides the presence of moderate to severe renal failure [17]. Decreased creatinine production due to decreased hepatic creatine synthesis may lead to a half raise in serum creatinine compared with non- cirrhotic population [18]. Increased tubular creatinine secretion and decreased skeletal muscle mass are additional factors that give rise to falsely low serum creatinine levels in patients with advanced liver disease. Unfortunately, serum creatinine is very insensitive to measure GFR with respect to the substantial decline in renal functions [16-20].

A number of laboratory methods are used to measure creatinine. Jaffe's reaction is routinely employed, but interferes with bilirubin, which may be higher in cirrhotic patients, resulting in falsely high serum creatinine values. There is evidence that different methods of creatinine measurement may affect MELD score [21]. A difference in MELD score higher than two points has been determined in about 60% of patients [21].

Serum creatinine is widely used for evaluation of renal functions, but on the account of mentioned reasons should be interpreted with caution in cirrhotic patients.

Creatinine Clearance

Creatinine clearance measurement from timed urine collections obviates some of the problems that appear when serum creatinine is used as a marker of GFR. Proulx *et al*. performed a review including seven studies of 193 patients. He and his co-workers reported that measured creatinine clearance overestimated inulin clearance by a mean of +13ml/min/1.73 m^2 and limits of agreement were +60 ml/min1.73 m^2 and -34 ml/min/1.73 m^2. This overestimation was highest in patients with lower GFR [23].

Although measured creatinine clearance from timed urine collections has been shown to overestimate GFR in patients with liver disease, two systematic reviews conclude that it is preferable in clinical practice because it provides a better estimatation than serum creatinine [17, 23].

Creatinine – Based Equations

The creatinine-based Cockcroft-Gault and the Modification of Diet in Renal Disease (MDRD) Study equations are commonly used in the general population for estimation of GFR [22,23]. Cockcroft-Gault equation requires weight, age and gender; in contrast, MDRD equation does not take into account the body weight variable, which is difficult to assess in cirrhotic patients with ascites, oedema and malnutrition. This formula is based on age, sex, serum Cr, albumin, ethnicity and urea nitrogen levels.

These equations have been validated in patients with end-stage renal disease (ESRD) [23] and in renal transplant recipients [24], but they have not been validated in either the cirrhotic or the post-liver transplant population. Skluzacek *et al*. [25] compared GFR calculated from renal clearance of iodine 125-labeled iothalamate (^{125}I-iothalamate) with the plasma decay technique and the Modification of Diet in Renal Disease (MDRD) and Cockroft-Gault (CG) prediction equations in a group of patients with liver cirrhosis evaluated for transplantation. They concluded that the current clinically used CG and MDRD equations to estimate kidney function in patients with cirrhosis and volume excess are inaccurate because they overestimate GFR. Recently, Mac Aulay *et al*. performed a study including fifty-seven subjects to compare calculations of GFR, using CGF and the MDRD formulas with standard radionuclide (99m-technetium-diethylenetriamine pent acetic acid - ^{99m}Tc-DTPA) measurement of GFR in patients with advanced liver disease (ALD) [26]. The study demonstrated that among the Cr-based GFR formulas, the MDRD formula showed a larger proportion of agreement with radionuclide GFR in patients with ALD. Authors recommended MDRD as the best formula for detection of moderate renal dysfunction among those with ALD. Gonwa *et al*. evaluated the performance of currently used formulas for the estimation of the GFR in 1447 patients who underwent liver transplantation. Only 66% of estimates were within 30% of the ^{125}I iothalamate measured GFR. The study illustrated that MDRD equations had greater precision than other equations, but the precision was lower than that reported for MDRD estimation of GFR in other populations [27].

All studies agreed that these equations overestimate GFR. The inaccuracy of creatinine-based Cockcroft-be relevant for several reasons. As mentioned previously, serum creatinine is an incorrect marker of Gault and the

Modification of Diet in Renal Disease (MDRD) Study equations in patients with cirrhosis may renal functions in this population. In this condition inaccuracy of createnine-based estimation of the GFR is not surprising. The difference in calibration of serum creatinine assays may be another reason. Because of these differences, it is difficult to make definite conclusions about the utility of equations based on creatinine measurement. Finally, current equations were derived from specific populations and may not be applicable in other populations of patients.

Cystatin C

Cystatin C is a low molecular weight protein produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus, not secreted but reabsorbed and metabolized in the tubules [28]. A number of studies determined cystatin C as a better marker of renal function than serum creatinine when compared with clearance of exogenous substances (e.g. inulin, ^{99m}Tc-DTPA, ^{125}I-iothalamate) [29]. In contrast to creatinine, serum cystatin C is independent of gender, age; muscle mass and serum concentration are not influenced by serum billirubin [30, 31]. Woitas *et al*. compared the reciprocal of cystatin C and serum creatinine with inulin clearance. They found a significant correlation between cystatin C and GFR measured by inulin clearance [33]. In thirty-six decompensate post-viral cirrhotic patients, Orlando *et al*. [34] reported that cystatin C was the most sensitive indicator of low GFR in cirrhotic patients. Several small studies suggested serum cystatin C as a preferable marker to assess renal functions [35-37]. A recent review from Francoz *et al*. [32] has emphasized that cystatin C assay is costly; needs further standardization; it is influenced by infection and by some drugs, such as corticosteroids, angiotensin-converting enzyme inhibitors or calcineurin inhibitors.

Equations to estimate GFR using cystatin C, which is suggested for application in patients with various renal disease, are evaluated in cirrhotic patients [38,39]. Poge *et al*. performed a study to evaluate the diagnostic accuracy of two cystatin C-based equations, such as Hoek and Larsson equations [38]. Data suggest a significant improvement of GFR estimation in cirrhotic patients by means of cystatin C-based Hoek and Larsson equations, but no one reached accuracy of the inulin clearance.

Although serum cystatin C is a better marker for estimating GFR than serum creatinine, this newer filtration marker needs to be verified in large populations.

Exogenous Markers for Measurement of GFR

Although renal clearance of inulin is the gold standard for GFR measurement, due to difficulty of administration and cost, its use in routine clinical practice is limited. Radiolabel compounds, such as ^{99m}Tc-DTPA, ^{125}I-iothalamate, ^{51}Cr-EDTA and non-radioactive iohexol or iothalamate are used as alternative exogenous filtration markers [40]. The most important advantages of these markers are a single-injection application and no need of urine collection. The use of radiolabel compounds is limited because of exposure to radiation and cost. Although relatively cumbersome, these filtration markers for GFR measurement are more accurate than those based on creatinine measurement. They are a mandatory feature of clinical trials, but not widely available in clinical practice.

Conclusion

Accurate measurement of GFR requires a clearance study using a validated filtration marker, such as iothalamate, iohexol, or inulin. Serum creatinine, as a component of MELD score, has a prognostic value in patients with liver disease, but due to several reasons it does not reflect the degree of renal dysfunction. Serum creatinine and the widely used creatinine-based equations must be interpreted with caution. Recent filtration markers for estimating GFR, such as cystatin C, should be verified in population of patients with liver diseases.

Conflict of interest statement. None declared.

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