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 bilirubin [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.
Inulin satisfies the criteria for an ideal clearance sub-
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 diffi-
culty of administration and cost, its use in routine clin-
cal practice is limited. Plasma creatinine level and endo-
genous 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 phos-
phocreatine, 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 cre-
atinine 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 con-
ditions that contribute to falsely low serum creatinine
concentrations, besides the presence of moderate to se-
vere 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 sec-
retion and decreased skeletal muscle mass are additional
factors that give rise to falsely low serum creatinine le-
vels in patients with advanced liver disease. Unfortu-
nately, serum creatinine is very insensitive to measure
GFR with respect to the substantial decline in renal func-
tions [16-20].

A number of laboratory methods are used to measure
creatinine. Jaffe’s reaction is routinely employed, but in-
terferes with bilirubin, which may be higher in cirrhotic
patients, resulting in falsely high serum creatinine valu-
es. There is evidence that different methods of creatini-
ne measurement may affect MELD score [21]. A differ-
rence 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 sho-
uld be interpreted with caution in cirrhotic patients.

**Creatinine Clearance**

Creatinine clearance measurement from timed urine col-
clections obviates some of the problems that appear
when serum creatinine is used as a marker of GFR. Pro-
ulx et al. performed a review including seven studies of
193 patients. He and his co-workers reported that me-
asured creatinine clearance overestimated inulin cle-
aranse by a mean of +13ml/min/1.73 m² and limits of
agreement were +60 ml/min1.73 m² and -34 ml/min/
stance since it is freely filtered at the glomerulus and is
1.73 m². This overestimation was highest in patients with
lower GFR [23].

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

**Creatinine – Based Equations**

The creatinine-based Cockcroft-Gault and the Modifi-
cation of Diet in Renal Disease (MDRD) Study equations
are commonly used in the general population for estima-
tion 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 asc-
cites, oedema and malnutrition. This formula is based
on age, sex, serum Cr, albumin, ethnicity and urea nitro-
gen levels.

These equations have been validated in patients with
end-stage renal disease (ESRD) [23] and in renal trans-
plant recipients [24], but they have not been validated in
either the cirrhotic or the post-liver transplant popula-
tion. Skluzacek et al. [25] compared GFR calculated from
renal clearance of iodine 125-labeled iothalamate
(¹²⁵I-iothalamate) with the plasma decay technique and
the Modification of Diet in Renal Disease (MDRD) and
Cockcroft-Gault (CG) prediction equations in a group of
patients with liver cirrhosis evaluated for transplantati-
on. They concluded that the current clinically used CG
and MDRD equations to estimate kidney function in pa-
ients 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-tech-
netium-diethylenetriamine pent acetic acid – ⁹⁹mTc-
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 radionu-
clide GFR in patients with ALD. Authors recommended
MDRD as the best formula for detection of moderate re-
nal 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 un-
went liver transplantation. Only 66% of estimates were
within 30% of the ¹²⁵I iothalamate measured GFR.
The study illustrated that MDRD equations had greater
precision than other equations, but the precision was lo-
wier 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, the creatinine-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 definitive 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 bilirubin [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]. Pogo 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.

**References**


