Original Research Article

A Hospital Based Prospective Study to Find Out Etiology of Chronic Liver Disease Has a Bearing on Renal Dysfunction

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Abstract

Background: Detection of renal insufficiency is clinically important because it contributes significantly to high morbidity and mortality in cirrhosis. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after transplantation, as compared with those without renal failure. The aim of this study to find out etiology of chronic liver disease has a bearing on renal dysfunction.**Materials & Methods:** The prospective study done on 50 patients admitted with chronic liver disease with seemingly normal renal function in department of Medicine at Shree Kalyan Government Medical College, Sikar, Rajasthan during one year period. The patients included with evidence for chronic liver disease being defined by a compatible Clinical profile along with Biochemical or Sonographic evidence OR Tissue diagnosis. Renal function was assessed by serum creatinine, creatinine clearance from timed urine collection [(UxV)/P] and creatinine clearance by Cockcroft Gault formula (CGF).**Results:** Our study showed that the mean value of age was 45.16 years. Of the patients included 40 were males, while remaining 10 were females. There was no significant variation in blood urea levels in all the three groups, suggesting that estimation of blood urea will not be of much use in determining renal impairment. Serum creatinine levels failed to rise above 1.2 mg/dL, suggesting that moderate to severe renal dysfunction may be masked by seemingly normal creatinine levels. Patients with greater amount of renal impairment were found to have lesser urine output, thus suggesting that eliciting history of oliguria in a patient with normal serum creatinine levels should call for a high index of suspicion of renal dysfunction. Measurement of creatinine clearance using the Cockcroft Gault formula (CGF) showed significantly higher values, suggesting overestimation of GFR by this method.**Conclusion:** We concluded that renal dysfunction in advanced liver disease, routine tests like blood urea and serum creatinine will be insufficient. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status.

Keywords: Chronic Liver Disease, Renal Disease, GFR, Serum Creatinine Clearance.

Introduction

Patients with advanced liver disease are susceptible to prerenal failure primarily due to disturbances in circulatory function- mainly, a reduction in systemic vascular resistance due to primary arterial vasodilatation in the splanchnic circulation, triggered by portal hypertension[1].Kidney dysfunction in liver disease can be due to different etiologies and can have diverse manifestations. Most of the abnormalities of kidney function in cirrhosis are of functional origin- namely, sodium retention, impaired free water excretion and renal vasoconstriction with decrease in renal perfusion and glomerular filtration rate. Renal dysfunction in chronic liver disease usually follows a progressive course – the final phase being Hepatorenal syndrome (HRS).

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The first description of disturbances in renal function in chronic liver diseases was made by Frerichs and Flint in two independent reports from the late nineteenth century[2]. The coexistence of renal impairment and liver disease has even been mentioned by Hippocrates[3]; Helwig and Schutz introduced the term hepatorenal syndrome in 1932 when they described a patient with renal failure and biliary tract disease[4].There is no explanation that fully defines the complex relationship between the diseased liver and disturbances in kidney function, though substantial progress is being made in recent years regarding research in this aspect.One of the most difficult issues in the clinical evaluation of patients with cirrhosis is the accurate assessment of renal function.Standard measures of renal function like blood urea nitrogen and serum creatinine are likely to give erroneous impressions and hence alternative methods to determine renal reserve must be used.Detection of renal insufficiency is clinically important because it contributes significantly to high morbidity and mortality in cirrhosis. Moreover, renal dysfunction is one of the most important risk factors when liver transplantation is being considered. Patients with cirrhosis and renal failure are at high risk for death while awaiting transplantation and have an increased frequency of complications and reduced survival after

transplantation, as compared with those without renal failure. The aim of this study to find out etiology of chronic liver disease has a bearing on renal dysfunction.

Materials & Methods

The prospective study done on 50 patients admitted with chronic liver disease with seemingly normal renal function in department of Medicine at Shree Kalyan Government Medical College, Sikar, Rajasthan during one year period. The patients included with evidence for chronic liver disease being defined by a compatible Clinical profile (signs of liver cell failure or reduced liver span) along with Biochemical (altered liver function tests, reversal of albumin-globulin ratio) or Sonographic evidence (altered echotexture of liver) or Tissue diagnosis (positive liver biopsy for cirrhosis).

Exclusion Criteria:

- Elderly patients (>60 years)
- Overt renal failure (S. creatinine >1.5)
- Known primary renal disease
- Diabetes mellitus / Hypertension
- Grade 4 hepatic encephalopathy
- Recent gastrointestinal bleed

Methodology: Data regarding demographic variables (age, weight), clinical features (presenting complaints, ascites, jaundice, encephalopathy, history of alcoholism, etc) and clinical examination findings of liver cell failure were collected using a proforma.

Diuretics were withheld for 3 days before carrying out lab investigations. Lab investigations including complete Liver function test, Renal function tests, Viral marker for hepatitis B, Urine analysis, 24 hour urine volume and Urine creatinine was done and results noted.Patients were subjected to an ultrasound scan of abdomen with regard to liver echotexture and size, evidence of splenomegaly or portal hypertension, presence of ascites and kidney pathology.Creatinine clearance for the patient was calculated by the formula(urine creatinine / serum creatinine multiplied by 24 hour urine volume).

$(U_{Cr} / P_{Cr}) \times V$

This was divided by 1440 to get the value in ml/minute. Creatinine clearance was also calculated using the Cockcroft and Gault formula (CGF).

(140- AGE) x WEIGHT / (SERUM CREATININE x 72)

This value is to be multiplied by 0.85 if the patient is female. Comparison between serum creatinine and creatinine clearance calculated by these two methods were done.

Renal function was assessed by serum creatinine, creatinine clearance from timed urine collection [(UxV)/P] and creatinine clearance by Cockcroft Gault formula (CGF).

The patients were grouped into three based on their creatinine clearance [(UxV)/P]. Group I having values more than 60 ml/mt, Group II 30-60 ml/mt and Group III less than 30 ml/mt.

Statistical analysis: Continuous variables were measured by chi-square test and student paired 't' test by SPSS 24 version.

Results

Our study showed that the mean value of age was 45.16 years. Of the patients included 40 were males, while remaining 10 were females (table 1).There was no significant variation in blood urea levels in all the three groups, suggesting that estimation of blood urea will not be of much use in determining renal impairment.Serum creatinine levels failed to rise above 1.2 mg/dL, suggesting that moderate to severe renal dysfunction may be masked by seemingly normal creatinine levels.Patients with greater amount of renal impairment were found to have lesser urine output, thus suggesting that eliciting history of oliguria in a patient with normal serum creatinine levels should call for a high index of suspicion of renal dysfunction.

Measurement of creatinine clearance using the Cockcroft Gault formula (CGF) showed significantly higher values, suggesting overestimation of GFR by this method (table 2).Out of the 25 alcoholic liver disease patients, only 6 (24%) had creatinine clearance more than 60 ml/minute, whereas 4 (57.14%) out of the 7 HBsAg positive patients had creatinine clearance more than 60 ml/minute (table 3).Serum albumin was found to have direct correlation with renal function, ie, patients with higher rates of creatinine clearance were seen to have higher albumin levels. Serum bilirubin levels were found to have no significant correlation with renal function (table 4)

Ultrasound abdomen was done in all of the 50 patients. Findings of splenomegaly and altered echotexture of liver were uniformly seen in all these patients. Ascites was present in 40 out of the 50 patients. It was noted that the patients without ascites had relatively better renal function; ie, all the 6 patients belonged to group I (Creatinine clearance > 60 ml/mt). thus, suggesting that ascites may be one of the first changes in worsening renal function.

Table 1: Demographic profile of patients

Demographic profile		No. of Patients (N=50)
Age (Mean±Sd) (Yrs)		45.16±9.73
Gender	Male	40 (80%)
	Female	10 (20%)

Table 2: Assessment Of Renal Function By Different Methods

Assessment of Renal function	Group I (CC>60ml/mt)	Group II (CC=30-60ml/mt)	Group III CC<30ml/mt)	P-value
Blood urea (mg/dl)	22.36±3.28	22.34±2.97	22.30±3.12	>0.05
Serum Creatinine (mg/dl)	0.98±0.67	1.02±0.70	1.20±0.93	>0.05
24 hour urine volume (ml)	2025.78±100.32	1153.80±87.64	712.56±78.38	<0.05*
Creatinine clearance (U×V/P) (ml/mt)	83.66±10.52	44.38±12.57	19.82±11.34	<0.05*
Creatinine clearance (CG formula) (ml/mt)	83.12±12.25	62.95±13.31	43.80±12.68	<0.05*

Table 3: Renal Function According To Etiology

Etiology	Group I (CC>60ml/mt)	Group II (CC=30-60ml/mt)	Group III (CC<30ml/mt)	Total
Alcoholism	6	12	7	25
Hepatitis B	4	3	0	7
Wilson's disease	0	0	1	1
Autoimmune	0	1	0	1
Unknown	7	7	2	16
Total	17	23	10	50

Table 4: Serum Albumin & serum Bilirubin and Renal Function

Etiology	Group I (CC>60ml/mt)	Group II (CC=30-60ml/mt)	Group III CC<30ml/mt)	p-value
Serum Albumin (mg/dl)				
>3.5	9	3	0	<0.05*
3.2-3.5	5	16	4	
<3.2	3	4	6	
Mean value	3.58	3.32	3.13	
Serum Bilirubin (mg/dl)				
<1.2	3	3	3	>0.05
1.2-2.0	10	14	4	
>2.0	4	6	3	
Mean value	1.68	1.62	1.65	

Discussion

Many patients with cirrhosis and ascites will have a glomerular filtration rate of less than 60 ml/minute but a normal serum creatinine level. Our study showed that serum creatinine alone in patients with advanced liver disease is of limited value for identification of renal dysfunction. This is in agreement with the findings in a study by McAulay et al[5]. Another prospective study of a large number of cirrhotic patients by Papadakis and Arieff also indicated that the glomerular filtration rate can be very low even when the serum creatinine is less than 1.0 mg/dl[6].Our study also shows that calculating creatinine clearance by Cockcroft Gault formula overestimates renal function. This is probably due to discrepancies in weight due to fluid retention which is one of the consequences of renal impairment in cirrhotics. As weight is one of the variables in the numerator of the formula, an increase in weight due to edema or ascites will give a spuriously high creatinine clearance. The study by McAulay also supports this finding[5]. This overestimation of renal function was highest in patients with lower GFR, which was observed in our study also.MacAulay et al[5] observed that among the Cr-based GFR formulas, the MDRD formula had the best overall accuracy. This formula developed by the Modification of Diet in Renal Disease (MDRD) Study Group is based on the patient's Creatinine levels, age, sex, race and serum urea nitrogen and serum albumin levels and it showed a larger proportion of agreement with radionuclide GFR in patients with advanced liver disease. MacAulay summarised that in clinical practice, the MDRD is the best formula for detection of moderate renal dysfunction among those with cirrhosis. But the above-mentioned study didn't include any formulas requiring urine collection. As MDRD formula requires web-based calculations, it will be impractical to rely on it as a parameter of assessing renal function in a resource limited setup.Measured creatinine clearance from timed urine collections is a relatively inexpensive, accessible method used in clinical practice. Our study showed that it provides a better estimate of renal reserve than serum creatinine or predicted creatinine clearance by Cockcroft-Gault formula.A systematic review and meta-analysis of patients with cirrhosis by Proulx et al showed that although creatinine clearance measured by timed urine collections overestimates GFR in patients with liver cirrhosis, it is a preferable method in clinical practice, as it is more reliable than serum creatinine or predicted creatinine clearance (by CGF)[7]. This overestimation is substantial especially in the low GFR range where important decisions relative to drug dose adjustment, the staging of CKD and the pre-liver transplant evaluation may be required.The meta-analysis proved that direct measurement of GFR using inulin clearance (CIn) is the most accurate estimate of renal reserve[8]. But in routine clinical practice, GFR estimation by this method is not very feasible because of the complexity, expense and limited availability of testing and overall patient inconvenience.The study by Papadakis and Arrief was a prospective evaluation of 23 non-azotemic cirrhotic patients with ascites over a three-year interval[6]. It showed that the serum creatinine levels frequently failed to rise above normal even when the glomerular filtration rate was very low (less than 25 ml/minute), and creatinine clearance overestimated inulin clearance. However, this study also suggested that creatinine clearance was an aid in determining true glomerular filtration rate (when inulin clearance was not available) and may be a useful clinical test in the evaluation of renal insufficiency in cirrhotic patients with normal serum creatinine values.Our study has shown a direct correlation between serum albumin levels and renal function. This may also indicate that renal dysfunction is more with advancing classes of Child-Pugh classification. The correlation with albumin levels has also been noted in a study by Amrapurkar et al[9].This latter study also denoted direct correlation between chronicity of liver disease and renal dysfunction. It also showed a higher mortality in patients with lower creatinine clearance especially with hepatorenal syndrome.But a study by Hampel et al showed no significant difference in serum levels of albumin and did not consider it as a risk factor for renal dysfunction[10]. The same study showed no significant differences in age, etiology of cirrhosis, serum levels of bilirubin, prothrombin time, encephalopathy, bacteremia, urinary tract infection, or occurrence of esophageal variceal bleeding in cirrhotic patients with or without renal dysfunction. Patients who developed renal dysfunction were more likely to have ascites. This was seen in our study also.The study by Hampel et al[10] also showed aminoglycoside treatment as a strong risk factor for renal dysfunction, independent of the severity of liver disease or spontaneous bacterial peritonitis.

Conclusion

Hence, to check for renal dysfunction in advanced liver disease, routine tests like blood urea and serum creatinine will be insufficient. Other methods like measured creatinine clearance should be employed to get an accurate picture of the renal status.

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