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ASSESSMENT OF RENAL DYSFUNCTION IN CHRONIC LIVER DISEASES

General Medicine

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ABSTRACT

Objectives: Renal impairment in Patients with chronic liver disease is a common phenomenon and is a functional impairment. It seems difficult for the assessment of renal function abnormalities by normal parameters. We aimed to determine the usefulness of creatinine clearance by timed urine collection and Cockcroft Gault formula and Serum creatinine as parameters in assessing renal function in this cohort of patients and also to find if etiology of chronic liver disease has a bearing on renal dysfunction.

Material and methods: Renal parameters of 200 patients with chronic liver disease were studied to assess the reliability of the each parameter.

Results: In the present study, Only 22% of alcoholics have clearance more than 60ml/min. 58% patients were found to have creatinine clearance more than 60ml/min by Cockcroft Gault formula while only 36% Patients have that by timed urine collection where the difference was found to be statistically significant (P value<0.01). Cockcroft Gault formula overestimates probably due to disparity in weight due to fluid retention.

Conclusion: The most reliable Parameter in our clinical setup is Creatinine clearance by timed urine collection. Presence of Ascites, low serum albumin levels and Alcoholic etiology had more predisposition to renal impairment, however, a larger study with more number of patients can throw more light.

KEYWORDS

Chronic liver diseases, creatinine clearance, renal.

INTRODUCTION:

The interrelationship between liver disease and renal dysfunction was recognized as early as the era of Hippocrates and this has been the object of a considerable amount of research since then.

The best known cause of azotaemia in patients with decompensated liver cirrhosis is functional vascular renal insufficiency, which is an indirect consequence of severe peripheral arterial vasodilation. Renal involvement is associated with steep rise in mortality and morbidity.

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. But 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. Renal dysfunction is one of the most important risk factors when liver transplantation is being considered.

AIMS AND OBJECTIVES:

To determine the usefulness of serum creatinine and creatinine clearance as parameters in assessing renal function abnormalities in patients with chronic liver disease.

PATIENTS AND METHODS:

1. **Study area:** Department of medicine, MAHARAJAH'S INSTITUTE OF MEDICAL SCIENCES (MIMS), Nellimarla, Vizianagaram.
2. **Study population**: The study was performed in MIMS amongst patients admitted to various medical wards and Intensive care unit.
3. **Study period**: One year (January 2017 to Dec 2017)
4. **Sample size:** A total of 200 adult cases of chronic liver disease (defined as hepatic injury lasting for at least 6 months and consist of two clinicoanatomic forms: cirrhosis and noncirrhotic portal hypertension[1]) constituted the material for the study.
5. **Sample design:** Having had informed consent for participation from the patient and/or patient care giver, the patient was included in the study according to following criteria.

INCLUSION CRITERIA:

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) whenever indicated.

EXCLUSION CRITERIA

a) Patients >60 years of age
b) Diabetes mellitus I Hypertension
c) Grade IV hepatic encephalopathy
d) Recent gastrointestinal bleed

Patients above 60 years were excluded as GFR decreases with age. False low GFR thus calculated could interfere with the findings of this study. Diabetes and Hypertension can impair renal function; hence cases with comorbidity with above two conditions were excluded. Similarly recent gastrointestinal bleed impairs renal function temporarily, hence excluded.

6. **Overview of data collection**: Data regarding history and clinical examination findings were collected using a proforma. Diuretics were withheld for 3 days before carrying out lab investigations. Patients were subject to an ultrasonogram of abdomen.

Creatinine clearance for the Patient was calculated by the formula
$= (U_{Cr} / P_{Cr}) \times V$

(This was divided by 1440 to get the value in ml/min)
U_{cr} = Urine creatinine
P_{cr} = Plasma creatinine
V = 24 hour urine volume

Creatinine clearance was also calculated using the Cockcroft 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) Serum creatinine values and creatinine clearance calculated by Cockcroft Gault formula were compared with timed urine collection.

OBSERVATIONS AND RESULTS:
200 Patients with chronic liver disease were enrolled in the year

Age: Age of patients ranged from 25 to 58 years with mean age of 41.88 years

Sex: They were 78% males and 22% females

Etiology: Alcoholic liver disease is the leading cause with 46% then as follows Hepatitis B (24%), Wilsons (2%), Autoimmune Hepatitis (4%) and unknown etiology constituted around 12%. Assessment of renal parameters was done after grouping into three based on their timed creatinine clearance value. (Table I)

Table I		
Group	**creatinine clearance**	**percentage of Patients**
Group I	>60 ml/min	34
Group II	30- 60 ml/min	40
Group III	<30 ml/min	13

Parameters in each group are drawn in table II

Mean blood urea was 22.20 mg/dl
Mean serum creatinine level was 1.12 mg/dl
Mean 24 hour urine volume was 1344 ml

Creatinine clearance was calculated by both CGF and times urine collection. 58% Patients were found to have creatinine clearance more than 60ml/min by CGF while only 36% Patients were found to have creatinine clearance more than 60 ml/min by timed urine collection.28% Patients with creatinine clearance more than 40 ml/min by Cockcroft fault formula were found to have creatinine clearance values less than 40 ml/min when done by timed urine collection. Difference was found to be statistically significant (P value <0.01)

Mean serum albumin in the present study was 3.32 mg/dl.
Mean bilirubin was 1.76 mg/dl
Ascites was present in 88% of the same population.

Table II			
Renal parameter (mean value of the group)	**group I**	**Group II**	**Group III**
Creatinine clearance (UxV/P) ml/min	74.72	41.59	22.69
Creatinine clearance (CGF) ml/min	82.85	60.96	52.34
Blood Urea (mg/dl)	22.12	22.30	22.15
Serum creatinine (mg/dl)	0.94	1.16	1.29
24 hour urine volume (ml)	1861.76	1250.71	811.54

DISCUSSION:
Males outnumbered females (78% males and 22% females).Maximum number of patients (84) was seen in the age group of 40 to 49 yrs., 40 patients were above the age of 50 years, 52 patients between 30-39 yrs. and 24 patients from less than 30 yrs. of age. The higher incidence of chronic liver disease among males could be due to prevalence of alcoholism in the male population.

All the Patients without Ascites (12%) were interestingly belonged to group I denoting better renal function, suggesting that Ascites may be one of the first changes in worsening of renal function. Similar kind of findings were observed in the studies done by Aggarwal et al[2] ,Arroyo V et al[3], Kashtan J at al[4], Mullens w et al[5], Umgelter A et al[6], Savino JA et al[7].

Only 22% of alcoholic liver disease patients had creatinine clearance of more than 60ml/min , whereas 33% of chronic Hepatitis B Patients had creatinine clearance of more than 60ml/min. These findings were consistent with the studies done by Grose RD et al[8], Wong F et al[9], Cecchin E et al[10], Keller F et al[11].

Significant correlation was found between serum albumin levels and renal function. Average serum albumin in Group I was 3.49 mg/dl , in group II was 3.31mg/dl and in group III was 3.09mg/dl. This observation was in parallel with studies done by Arroyo V at al[3], Umgelter et al[6].

Our study showed that standard measures of renal function, namely blood urea and serum creatinine should not be the only criteria to assess renal reserve in chronic liver disease, as they may seem normal even in gross renal dysfunction. Generally, the creatinine level is not a perfect indicator of renal function as it is influenced by many nonrenal factors (e.g., body weight, age, sex, race and blood volume), shows a nonlinear relationship with GFR and does not distinguish between functional and organic renal diseases. The creatinine levels in patients with end-stage cirrhosis regularly underestimate the actual GFR because of decreased hepatic production of creatine and muscle wasting. An additional factor responsible for low serum creatinine in decompensated cirrhosis is hypervolemia. Our study showed that many patients with decompensated liver disease had GFR of less than 60 ml/minute but a normal serum creatinine level. It was seen that in 20 patients with creatinine clearance less than 30 ml/min, serum creatinine levels failed to rise above 1.2 mg/dL. Hence serum creatinine alone in patients with advanced liver disease is of limited value for identification of renal dysfunction. The above is in agreement with the findings in studies done by Francoz C et al[12], Ginés P et al[13], Takabatake T et al[14], Slack AJ et al[15], Papadakis M Aet al [16] , McAulay J et al[17].

The level of serum creatinine required for the diagnosis of HRS is 1.5 mg/dL, in the absence of diuretic therapy. Although this value may seem rather low, patients with cirrhosis and a serum creatinine above 1.5 mg/dL have a GFR below 30 ml/min. Hence, patients with creatinine levels more than 1.5 mg/dL were excluded from our study.

But in a study done by Cholangitas E et al[18], serum creatinine was one of the three variables that formed the model of end stage liver disease (MELD Score) that predicts 3-month survival in patients with end-stage cirrhosis. In the MELD score, creatinine was assigned a much higher and probably excessive weightage than bilirubin.

Our study showed 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 above results were comparable with studies done by MacAulay J et al[17], Michels WM et al[19], Earley et al[20], Vukobrat-Bijedic et al[21], Poggio et al[22], Skulzacek PA et al[23]. So measured creatinine clearance from timed urine collection provides a better estimate of renal reserve than predicted creatinine clearance by Cockcroft-Gault formula. However, A systematic review and meta-analysis of patients with cirrhosis by Proulx et at [24] showed that Timed urine creatinine clearance also performs poorly, significantly overestimating GFR in patients with chronic liver disease, particularly at the lower range of GFR measurements. But it is a preferable method in clinical practice at limited lab set up.

MacAulay et al [17] and Poggio et al[22] observed that among the Creatinine 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 level, 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.

Studies like Herget-Rosenthal S et al[25], Parikh CR et al[26], Han WK et al[27], Mishra J et al[28] supported the use of like Serum neutrophil gelatinase lipocalin (sNGAL), Serum cystatin C, urinary Kidney injury molecule 1 (KIM-1), urinary interleukin-18 (IL-18) and urinary NGAL (uNGAL) to assess renal function in patients with liver cirrhosis, which again will be impractical in our setup.

LIMITATIONS:
Though timed urine collection method gives more reliable result than the other two methods (serum creatinine level and Cockcroft Fault formula), it is not without limitations since this method overestimates GFR in patients of chronic liver disease particularly at the lower levels of glomerular filtration rate. More advanced methods like

radionucleotide method, lnulin clearance test are more accurate, and however they are impractical in our setup.

CONCLUSION AND SUMMARY:

Presence of ascites is associated with renal dysfunction in cirrhosis. Alcoholism appears to have adverse effect on renal function when compared to other etiologies. Blood urea and serum creatinine are not reliable markers to assess renal dysfunction. Creatinine clearance calculated using Cockcroft Gault formula overestimates renal function in cirrhosis and it was statistically significant. It was found that measurement of creatinine clearance from timed urine collections is a relatively inexpensive, accessible method for clinical practice and should be done routinely to assess renal reserve in advanced liver disease. It was observed that Patients with higher albumin levels were seen to have higher rates of creatinine clearance.

A larger study with more number of patients can throw more light.

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