LIVER FUNCTIONS IN UREMIA AND AFTER TREATMENT BY REGULAR HEMODIALYSIS

THESIS

Submitted in Partial Fulfillment
For the Master Degree in
INTERNAL MEDICINE

Presented By

Dr. Hesham Abd-El Raouf Ali

M.B.B.Ch

Supervised By

Prof. WAHID EL-SAID
Professor of Internal Medicine
Faculty of Medicine
Ain Shams University

Prof. FADILA HASSAN SABRY
Professor of Clinical Patholcgy
Faculty of Medicine
Ain Shams University

Dr. MAHMOUD ABD-EL-FATTAH
Lecturer of Internal Medicine
Faculty of Medicine
Ain Shams University

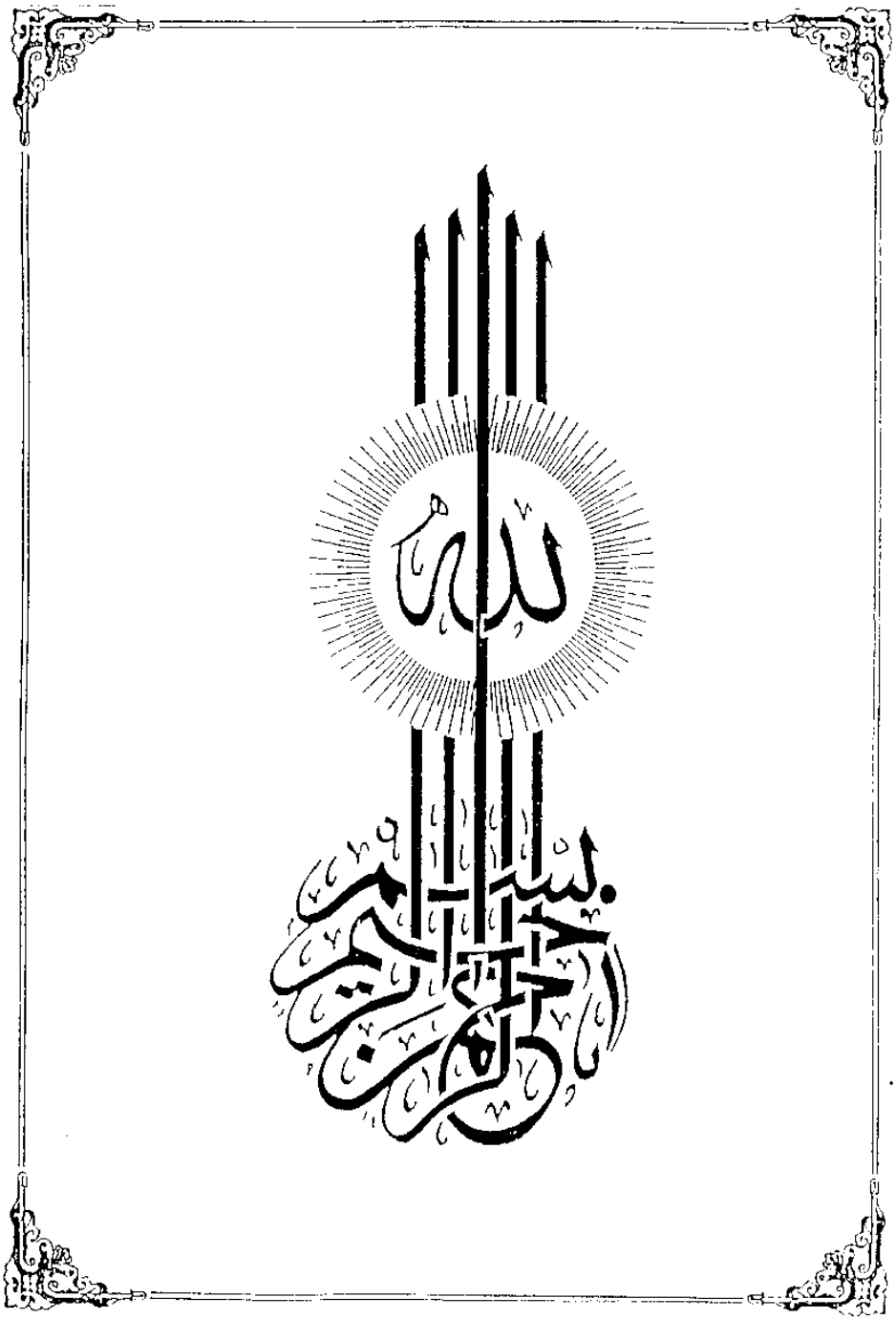
Faculty of Medicine
Ain Shams University

1986

بسم الله الرحمن الرحيم

وما اوتيتم من العلم إلا قليلاً

سورة الإسراء (آية ٨٥)



CONTENTS

INTRODUCTION

AIM OF THE WORK

AIM OF THE WORK

The aim of this work is to study the effect of uremia on liver functions and the effect of a single hemodialysis session on liver functions in patients with chronic renal failure submitted to this type of treatment.

REVIEW OF LITERATURE

LIVER DISEASES THAT AFFECT RENAL FUNCTIONS
THE HEPATORENAL SYNDROME (HRS)

Progressive oliguric renal failure commonly complicates the course of patients with advanced hepatic disease. While this condition has been designated by many names including *"Functional renal failure"*, and *"The renal failure of cirrhosis"*, the more appealing, albeit less specific, term *"hepatorenal syndrome"* (HRS) has been used. Hepatorenal syndrome may be defined as unexplained renal failure occurring in patients with liver disease in the absence of clinical, laboratory, or anatomic evidence of other known causes of renal failure *(Epstein, 1983)*.

The clinical presentation and course of HRS are characterized by marked variability. The HRS occurs usually in cirrhotic patients who are alcoholic, but also may develop in patients with acute hepatitis and hepatic malignancy *(Epstein, 1983)*. Renal failure may develop with great rapidity, occasionally occurring in patients in whom normal GFR and concentrating ability have been previously documented a few days before the onset of HRS. It can occur in the absence of an apparent precipitating factor *(Epstein, 1983)*. HRS and portal hypertension may develop in patients with chronic lymphocytic leukemia *(Papadakis et al., 1986)*.

Rarely, HRS can occur with little evidence of severe hepatic dysfunction. The degree of jaundice is extremely variable, and, occasionally, renal failure may develop at a time when the serum bilirubin concentration is decreasing. Most patients have a modest decrease in systemic blood pressure, urine volume is reduced (less than 800 ml/day), oliguria is common (less than 500 ml/day), but anuria is rare *(Epstein, 1983)*.

The serum creatinine and blood urea nitrogen are elevated but seldom approach the high values seen in patients with end-stage renal failure due to primary

renal disease. The urine is usually acid; mild proteinuria, granular casts, and microscopic hematuria are not infrequent. The urine is virtually sodium-free (less than 10 mEq of Na^+/L) and modestly concentrated. Towards the end of the clinical course, urinary sodium excretion may increase and urine osmolality approaches isotonicity *(Epstein, 1983)*.

The hepatorenal syndrome, a primary cause of death from acute and chronic liver disease, consists of a functional renal failure where by examination of the kidneys has previously shown no distinct or specific morphologic change *(Kanel and Peters, 1984)*.

Pathological abnormalities are minimal and inconsistent. Furthermore, tubular functional integrity is maintained during the renal failure. More direct evidence is derived from the demonstration that kidneys transplanted from patients with HRS are capable of resuming normal function in the recipient *(Epstein, 1983)*.

In severe liver failure, deficient secretion of the liver hormone that increases glomerular filtration rate is presumed to cause or contribute to the development of the HRS *(Alvestrand and Bergstrom, 1984)*.

Unusual renal lesion consists of the reflux of proximal convoluted tubular epithelium into Bowman's space. An autopsy series shows this glomerular change to be present in 71.4% of cases with the hepatorenal syndrome, while only present in 0 to 27.3% in other autopsy categories. Since this lesion has been previously described with experimental renal ischemic change and terminal hypotension, it is possible that it is caused in part by the decreased or altered renal blood flow known to be associated with the hepatorenal syndrome *(Kanel and Peters, 1984)*.

Acute tubular necrosis of variable severity may be associated with the hepatorenal syndrome. It develops without preceding shock, sepsis, or hypotension.

But it is possible, like that in ischemic acute renal failure, that it may be due to reduced renal blood flow and intense cortical vasoconstriction which has been reported in hepatorenal syndrome *(Mandal et al., 1982)*.

Tubular dysfunction, manifested by increased urinary excretion of β_2-microglobulin, occurs in patients with hepatorenal syndrome and deep jaundice *(Rector et al., 1985)*.

Pericarditis was observed in five patients with decompensated cirrhosis who had only slightly raised blood-urea-nitrogen and serum-creatinine *(Wise et al., 1980)*.

Patients with decompensated cirrhosis with or without HRS frequently manifest marked elevations of plasma renin activity (PRA) attributable to both decreased hepatic inactivation of renin and to increased renin secretion by the kidney. Often, the elevation of PRA occurs despite the presumed failure of hepatic synthesis of the α_2-globulin renin substrate *(Epstein, 1983)*.

There are at least two alternative explanations for the persistence of high PRA in cirrhosis.First, it is possible that the renal hypoperfusion is the primary event with a resultant activation of renin-angiotensin system *(Epstein, 1983 - Cobden et al., 1985)*. Alternatively, the activation of the renin-angiotensin system, perhaps in response to a diminished effective blood volume, may constitute the main pathogenic factor *(Epstein, 1983)*.

The role of prostaglandins in the genesis of HRS is not established. Inhibition of prostaglandin synthesis with indomethacin or ibuprofen was followed by a marked decline in GFR. This raises the possibility that an impairment of the ability of the kidney to augment PGE synthesis may be involved in the development of HRS *(Epstein, 1983)*.

Intrarenal prostaglandin E_1 failed to increase urine volume or urinary sodium concentration in three patients with the hepatorenal syndrome *(Zusman et al., 1977)*.

Measurements of plasma prekallikrein levels in patients with HRS disclosed undetectable levels in many such patients, raising the possibility that the decrease in prekallikrein levels results in diminished kinin formation. Since bradykinin has been suggested to be a physiological renal vasodilator, it is possible that failure of bradykinin formation may contribute to the renal cortical vasoconstriction encountered in HRS. Endotoxins might contribute to the pathogenesis of HRS *(Epstein, 1983)*.

Hemodialysis and peritoneovenous shunting have potential values in patients with advanced hepatorenal syndrome *(Kearns et al., 1985)*.

In hepatorenal syndrome, captopril in standard dosage is without benefit, and provides further evidence that the changes in the renin-angiotensin system are probably secondary to reduced renal perfusion from some other cause *(Cobden et al., 1985)*. Reversal of the morbid hepatorenal syndrome has been achieved in a cirrhotic patient with ascites following successful side-to-side portocaval shunt *(Ariyan et al., 1975)*.

CIRRHOSIS OF THE LIVER

Cirrhosis is an irreversible alteration of the liver architecture, consisting of hepatic fibrosis and areas of nodular regeneration. When the nodules are small (less than 3 mm), uniform, and encompass one lobule, the term micronodular or unilobular cirrhosis is applied. In macronodular or multilobular cirrhosis, the nodules exceed 3 mm, vary in size, and encompass more than one lobule. Frequently, features of both micro- and macronodular cirrhosis are present in the same liver *(Boyer, 1985)*.

Alcoholic liver disease is a serious sequela of the chronic abuse of ethanol. There are three histopathologic lesions associated with ethanol abuse; fatty liver, alcoholic hepatitis, and cirrhosis.

Primary biliary cirrhosis is a cholestatic disorder that develops because of progressive destruction of small and intermediate-sized intrahepatic bile ducts. The extrahepatic biliary tree and large intrahepatic bile ducts are patent. The cause of primary biliary cirrhosis is unknown.

Secondary biliary cirrhosis is an uncommon sequela of longstanding obstruction of the biliary tree. Obstruction is usually present for more than one year before cirrhosis develops. The liver is usually enlarged and dark green in color. The surface is granular or occasionally nodular.

Cardiac cirrhosis is an uncommon complication of severe, prolonged, recurrent right sided heart failure. The gross appearance of the liver in acute hepatic failure is one of alternating red and pale areas (nutmeg liver).

Cryptogenic (macronodular or postnecrotic) cirrhosis is any cirrhosis for which the etiology is unknown. The liver contains little or no necrosis or inflammation and has no diagnostic pathologic lesions *(Boyer, 1985)*.

In patients with liver disease, serum-sodium levels below 130 mEq per litre must be regarded as serious, and, if below 125 mEq per litre, ominous *(Hecker and Sherlock, 1956)*.

Renal Involvement in Liver Cirrhosis

Renal glomerular changes with liver diseases of various etiology have been defined as *hepatic glomerulosclerosis* of non-inflammatory origin. Recently, the nephropathy of liver disease had been defined by "WHO Committee for the Classification of Renal Diseases" as structural abnormalities of glomeruli found in patients with hepatitis and with liver cirrhosis, consisting of mesangial proliferation and sclerosis, or in more severe cases, mesangio-capillary or membranous nephropathy *(Sinniah., 1984)*.

In cases of liver cirrhosis, there was a variable glomerular morphology including normal appearance by light microscopy (32%), minor changes (38.7%), diffuse mesangial sclerosis (12%), diffuse mesangial cell proliferation, and infrequently membranous and diffuse proliferative glomerulonephritis with a "lobular pattern". The cirrhotic glomerulonephropathy was usually clinically latent *(Sinniah, 1984)*.

The heterogenous glomerulonephropathy of liver cirrhosis has commonly been called cirrhotic glomerulonephropathy, and was usually clinically insignificant. In severe cases, pronounced proteinuria, slight hematuria, and granular casts were observed. Patients with mesangio-capillary glomerulonephritis associated with liver cirrhosis were more likely to have symptoms and present with a nephrotic syndrome *(Sinniah, 1984)*.

Mesangio-capillary glomerulonephritis has no specific etiological cause, but represents a specific immunological reaction to a wide variety of antigens. The

mesangio-capillary glomerulonephritis occurring with liver cirrhosis may be an autoimmune response against antigens from the gastrointestinal tract. The other types of cirrhosis-associated glomerular lesions were more likely to have sub-clinical renal disease *(Sinniah, 1984)*. The association of primary biliary cirrhosis, cutaneous vasculitis, and membranous nephropathy has been reported (*Glassock et al., 1986)*.

Mean renal blood flow was often reduced in cirrhotic patients with normal blood-urea, and this was usually associated with a redistribution of intrarenal blood-flow, the distribution to and flow-rate through the outer cortex being reduced while juxtamedullary and medullary flow was maintained. The presence of these renal circulatory changes may explain why patients with hepatic cirrhosis readily develop oliguric renal failure in response to minor decreases in circulatory blood volume or shifts of fluid within body compartments *(Kew et al., 1971)*.

In patients with cirrhotic ascites who develop end-stage renal failure, successful long-term management can be obtained using a combination of peritoneo-venous shunting and maintenance hemodialysis *(Gandhi et al., 1985)*.

Cirrhotics with renal failure showed a significantly higher renin and norepinephrine, and a significantly lower urinary kallikrein and urinary prostaglandin E_2 than did normal subjects and cirrhotics without renal failure. Glomerular filtration rate correlated with urinary kallikrein, urinary prostaglandin, plasma renin and norepinephrine (*Perez-Ayuso et al., 1985)*.

The assumption of upright posture by patients with liver cirrhosis leads to striking activation of adrenergic and renin-angiotensin systems resulting in rise of basal plasma renin activity, aldosterone, and noradrenaline concentrations *(Bernardi et al., 1985)*.