CHAPTER 1

LIVER CELL FAILURE AND KIDNEY DYSFUNCTION

Surgical anatomy of the liver:

The liver is the second largest (after the skin) organ in the human body and the largest gland (weighing an average of 1500 g). It lies under the diaphragm in the right upper abdomen and mid abdomen and extends to the left upper abdomen. The liver has the general shape of a prism or wedge, with its base to the right and its apex to the left. It is pinkish brown in color, with a soft consistency, and is highly vascular and easily friable ***(Gray and Lewis, 2000).***

The falciform ligament divides the liver into two parts, termed the right and left lobes. The right lobe is much larger and contains the caudate and the quadrate lobes. The liver depends on a dual blood supply, the hepatic artery and the portal vein, and it is drained through the hepatic veins. The liver is organized into hepatic lobules. Each lobule is typically hexagonal in cross section and is centered on a branch of the hepatic vein ***(Skandalakis et al., 2004).***

In the most usual surgical classification in North America, the portal venous supply of the liver defines eight sub-segments of the liver. The boundaries of these segments are

grossly defined by the hepatic veins (in the cranio-caudal direction) and by the plane of the portal vein which is horizontal on the right, oblique on the left ***(Solomon and Aragon, 2012).***

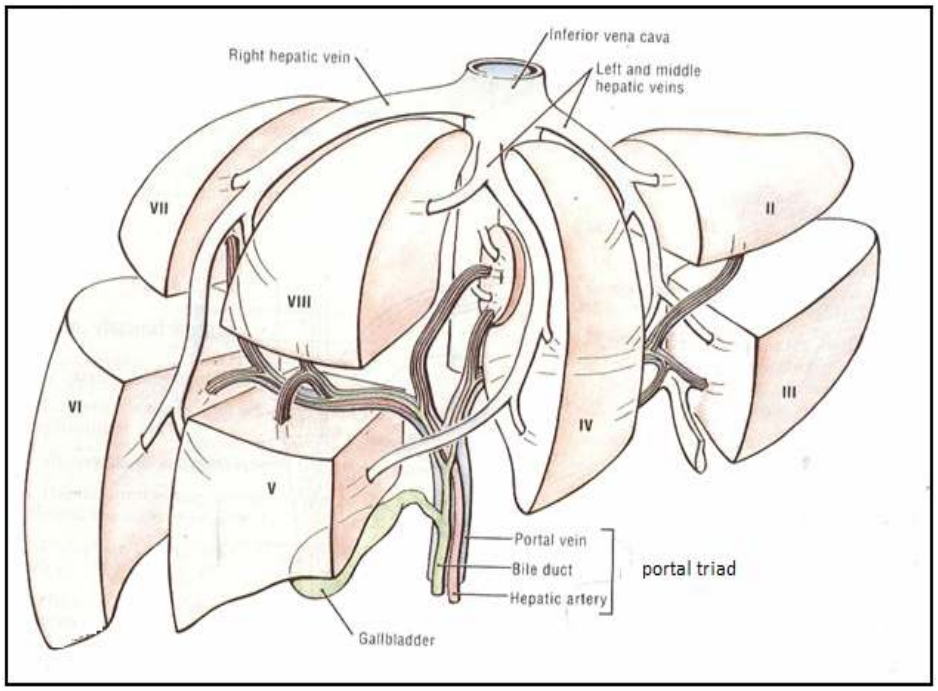

Figure (1): View of liver shows relation between intrahepatic vessels and liver segments (I-VIII) ***(Solomon and Aragon, 2012).***

Liver cirrhosis:

Cirrhosis represents the final common histological pathway for a wide variety of chronic liver diseases and insults. It is defined as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Its most important causes are:

- Hepatitis C (leading cause of liver cancer and cirrhosis)
- Alcoholic liver disease
- Cryptogenic causes (Many cases actually are due to nonalcoholic fatty liver disease)
- Hepatitis B, which may be coincident with hepatitis D
- Hereditary hemochromatosis
- Miscellaneous

The fat-storing stellate cells in the space of Disse, appears to be the source of excess collagen deposition in the liver ***(Ramadori et al., 2008).***

Renal failure is a challenging complication of cirrhosis and 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 ***(Nair et al., 2002).***

In 2002, the Model for End-Stage Liver Disease (MELD) score — derived from measurements of serum bilirubin, the international normalized ratio of prothrombin time, and serum creatinine to evaluate pretransplantation renal function — was introduced as an aid to organ allocation among candidates for liver transplantation. Use of this scoring system has increased

the number of patients with renal failure who receive a liver transplant and has reduced mortality among patients awaiting liver transplantation ***(Kamath et al., 2007).***

The MELD score was validated as an accurate predictor of survival among different populations of patients with advanced liver disease. However, the major use of MELD score is in allocation of organs for liver transplantation ***(Wiesner et al., 2003).***

Pathophysiology of Renal affection with liver diseases

There is considerable evidence that renal failure in patients with cirrhosis is primarily related 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 ***(Ginès et al., 2007).***

The cause of this arterial vasodilatation is increased production or activity of vasodilator factors particularly nitric oxide, mainly in the splanchnic circulation ***(Bosch et al., 2008).***

In advanced cirrhosis, arterial pressure must be maintained through the activation of vasoconstrictor systems, including the renin–angiotensin system, the sympathetic nervous system, and in late stages, hypersecretion of arginine vasopressin (antidiuretic hormone). These compensatory mechanisms help maintain effective arterial blood volume and

relatively normal arterial pressure but have important effects on kidney function, particularly sodium and solute-free water retention, that may eventually lead to ascites and edema and to renal failure by causing intrarenal vasoconstriction and hypoperfusion ***(Arroyo et al., 1996).***

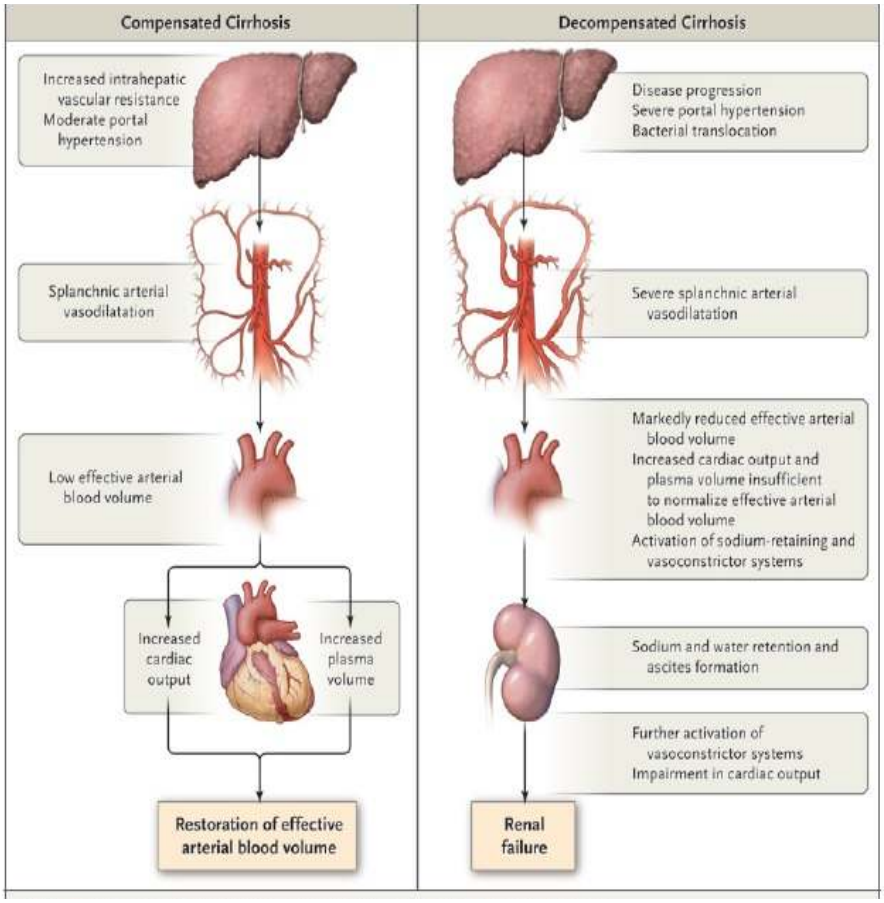

Figure (2): Pathogenesis of circulatory abnormalities and renal failure in cirrhosis ***(Ginès and Schrier, 2009).***

With broadening of the inclusion criteria for liver transplantation, the majority of liver transplant recipients have some impairment of renal function prior to transplantation and most have clinically apparent renal insufficiency at some time in the post-transplant period, among those with renal impairment at the time of transplant are patients whose renal failure is due to the same underlying process that caused the liver disease (hepatitis B, hepatitis C, analgesic overdose, amyloidosis, autoimmune disease), patients with underlying parenchymal renal disease from diseases such as diabetes and hypertension, and other patients in whom the functional renal impairment is caused by the liver failure itself and its complications ***(Smith, 2006).***

The risk of developing renal failure increases as the severity of liver disease worsens. The etiology of kidney injury in cirrhotic patients can be classified as prerenal, intrarenal or postrenal. In cirrhotic patients with ascites, pre-renal failure (42%) and acute tubular necrosis (ATN) (38%) represent the most common forms of acute renal failure while hepatorenal syndrome (HRS) is somewhat less frequent (20%) ***(Fasolato et al., 2007).***

1. Volume depletion induced renal dysfunction

The principle cause of prerenal injury is hypoperfusion. A failure to adequately perfuse the kidney in cirrhosis is often related to hypovolemia caused by adverse events such as

gastrointestinal bleeding, severe sepsis or excessive diuretic therapy. However, renal hypoperfusion can also occur in decompensated cirrhosis in the absence of complications associated with portal hypertension ***(Moreau and Lebrec, 2008).***

Prerenal failure usually occurs in patients with decompensated cirrhosis. These patients already have significant circulatory dysfunction characterized by low arterial pressure, renal vasoconstriction and decreased renal blood flow; but they have no or only mild reduction in glomerular filtration rate (GFR). Volume depletion further decreases renal blood flow and induces a marked decline in GFR which may be rapidly reversible if the underlying cause is corrected. True hypovolemia and subsequent renal failure may also result from vomiting, diarrhea, glycosuria or diuretic treatment used to mobilize ascites. This true hypovolemia is one cause of prerenal azotemia ***(Moreau and Lebrec, 2003).***

Patients admitted for hemorrhage may also develop prerenal failure due to other causes such as bacterial infection ***(Cardenas et al., 2001).***

2. Severe sepsis

Patients with cirrhosis are susceptible to bacterial infections, in particular spontaneous bacterial peritonitis (SBP). Septic shock and subsequent prerenal azotemia occurs with SBP. At the onset of SBP, 20-40% of patients have renal failure without shock ***(Moreau and Lebrec, 2006).***

3. Viral hepatitis induced renal impairment

Viral infections such as hepatitis B (HBV) and C (HCV) are well-known to induce concomitant severe hepatic and renal injuries with ultimate end-stage renal disease. Hepatitis C has long been associated with several glomerulopathies, most notably cryoglobulin- and non-cryoglobulin – associated membranoproliferative glomerulonephritis. In seropositive hepatitis C populations, hepatitis C infection has been reported to be associated with focal segmental glomerulosclerosis, membranous nephropathy with or without nephrotic range proteinuria, IgA nephropathy, and proliferative glomerulonephritidies ***(Sabry et al., 2002).***

Hepatitis B virus (HBV) is also with a number of renal diseases, including polyarteritis nodosa, membranous and membranoproliferative glomerulonephritis. Most patients have a history of active HBV but are asymptomatic with positive surface antigen and core antibody; in those with membranous nephropathy, e antigen is positive. The pathogenic role of HBV has been demonstrated by the presence of antigen-antibody complexes in kidney biopsy specimens and in particular deposition of HBVe antigen in membranous glomerulonephritis ***(Appel, 2007).***

4. Congenital diseases affecting liver and kidney

Autosomal-dominant polycystic kidney disease is associated with polycystic liver disease in up to 75-90% of cases. Most patients are asymptomatic, but when symptoms do occur, they are often related to cyst size and number. Symptoms include abdominal pain, nausea, early satiety, breathlessness, ascites, and biliary obstruction. The medical complications seen with autosomal-dominant polycystic kidney disease including intracranial aneurysms, and valvular heart lesion are also encountered in those with cystic liver disease ***(Russel et al., 2007).***

5. Hepatorenal syndrome

Hepatorenal Syndrome (HRS) is a form of prerenal acute kidney injury that occurs in decompensated cirrhosis. The diagnosis is based on the exclusion of other causes of renal injury. Affected patients usually have portal hypertension due to cirrhosis, severe alcoholic hepatitis, or (less often) metastatic tumors, but can also have fulminant hepatic failure from any cause. The hepatorenal syndrome represents the end-stage of a sequence of reductions in renal perfusion induced by increasingly severe hepatic injury. The hepatorenal syndrome is a diagnosis of exclusion and is associated with a poor prognosis ***(Wadei et al., 2006).***

Arterial vasodilatation in the splanchnic circulation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in cirrhosis]. The presumed mechanism is

increased production or activity of vasodilators, mainly in the splanchnic circulation, with nitric oxide thought to be most important ***(Ginès and Schrier, 2009).***

As the hepatic disease becomes more severe, there is a progressive rise in cardiac output and fall in systemic vascular resistance; the latter change occurs despite local increases in renal and femoral vascular resistance that result in part from hypotension-induced activation of the renin-angiotensin and sympathetic nervous systems ***(Wadei et al., 2006).***

The following definition and diagnostic criteria have been proposed for the hepatorenal syndrome:

1. Chronic or acute hepatic disease with advanced hepatic failure and portal hypertension.
2. A serum creatinine above 1.5 mg/dL (133 micromol/L) that progresses over days to weeks (ie, acute or subacute kidney injury). The rise in serum creatinine with reductions in glomerular filtration rate (GFR) may be minimal due to the marked reduction in creatinine production among such patients.
3. The absence of any other apparent cause for the acute kidney injury, including shock, current or recent treatment with nephrotoxic drugs, and the absence of ultrasonographic evidence of obstruction or parenchymal renal disease. Spontaneous bacterial peritonitis is complicated by acute kidney injury that may be

reversible in 30 to 40 percent of patients. It can be associated with ATN, but it is also a major precipitant of the hepatorenal syndrome. Thus, ongoing infection with spontaneous bacterial peritonitis should not exclude the possibility of hepatorenal syndrome. This means that therapy for hepatorenal syndrome can commence while the bacterial infection is still being treated.

4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. Absence of signs of parenchymal renal disease, as suggested by proteinuria (500 mg/day) or hematuria (50 red blood cells per high-power field), and/or abnormal renal ultrasound.

(Salerno et al., 2007)

However, not all patients with hepatorenal syndrome have oliguria (especially early in its course), a progressive rise in serum creatinine, and a benign urine sediment. Urine volumes may be higher than previously appreciated. Some studies, for example, have found that the urine volume may exceed 400 mL per day, with markedly lower output being observed only within a few days from death ***(Esraillian et al., 2007).***

Based upon the rapidity of the decline in kidney function, two forms of hepatorenal syndrome have been described:

- **Type 1 hepatorenal syndrome** is the more serious type; it is defined as at least a twofold increase in serum creatinine (reflecting a 50 percent reduction in creatinine clearance) to a level greater than 2.5 mg/dL (221 micromol/L) during a period of less than two weeks. At the time of diagnosis, some patients with type 1 hepatorenal syndrome have a urine output less than 400 to 500 mL per day

- **Type 2 hepatorenal syndrome** is defined as renal impairment that is less severe than that observed with type 1 disease. The major clinical feature in patients with type 2 hepatorenal syndrome is ascites that is resistant to diuretics ***(Salerno et al., 2007)***

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 ***(Durand et al., 2005).***

Assessment of Renal Functions:

For both prognostic and therapeutic reasons it is important to assess the level of renal function in patients being considered for liver transplantation and to determine if there is any reversible component. Also given organ shortage it should be essential to determine which patients will experience progressive and severe renal dysfunction after liver transplantation ***(Burra et al., 2009).***

The most commonly used markers of glomerular filtration rate (GFR), blood urea nitrogen (BUN) and serum creatinine, have limitations that should be kept in mind, especially in the setting of liver transplantation. Because urea is generated by the liver from the metabolism of protein and ammonia, both malnutrition and poor hepatic function may cause a falsely low BUN that can lead to an overestimation of GFR. Conversely, corticosteroids, bleeding (particularly in the gastrointestinal tract), and renal hypoperfusion cause higher BUN levels than one would expect for a given level of GFR ***(Cholongitas et al., 2007).***

1. Serum creatinine

Also current diagnostic paradigms for acute kidney injury are limited by reliance on serum creatinine (S.Cr) which is affected by age, gender, nutrition and the amount of muscle mass which may render the values inaccurate. Thus, most

patients with endstage liver disease with decreased muscle mass may have a misleadingly low S.Cr. In addition, elevations in S.Cr. may occur several days after the actual injury ***(Fieghen et al., 2009).***

Furthermore, creatinine is both filtered and secreted by the nephron, so that its clearance is an overestimate of GFR. It should also be noted that the relationship between the serum creatinine and GFR is not linear; at high levels of GFR, the S.Cr is insensitive to large changes in GFR, while at low levels of GFR, small changes in GFR cause large changes in serum creatinine ***(Mariat et al., 2004).***

Serum creatinine is usually measured by the Jaffè method, but this is prone to interference, for example, from protein, ketones and bilirubin. Hence, hyperbilirubinemia often impacts on the measurement of Scr in endstage liver disease population ***(Owen et al., 2006).***

Despite the above limitations, the endogenous creatinine clearance from a timed urine collection or as calculated from the Cockcroft–Gault formula {(140- age)/Cr × (weight in kg/72) (× 0.85 for females)} (Cockcroft and Gault, 1976) remains the most common measure of GFR ***(Lewandowska and Matuszkiewicz-Rowinska, 2011).***

2. Timed urine collection measurement of 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. 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 estimation than serum creatinine ***(Sherman et al., 2003).***

3. Novel biomarkers

More than 20 different biomarkers have been identified in recent years, However, most current focus is on neutrophil gelatinase associated lipocalin (NGAL) and cystatin-C. At present these remain experimental and need validation in larger studies prior to transition into clinical practice ***(Coca et al., 2007).***

- **NGAL**

Neutrophil gelatinase-associated lipocalin (NGAL) protein is a novel biomarker which is almost undetectable in either urine or plasma in patients with normal renal function but easily detected in the blood and urine soon after AKI ***(Mishra et al., 2003).***