Introduction

Liver cirrhosis is an increasing cause of morbidity and mortality in more developed countries, being the 14th most common cause of death worldwide. Increasingly, cirrhosis has been seen to be not a single disease entity, but one that can be subclassified into distinct clinical prognostic stages **(Schuppan D et al., 2008).**

Cirrhosis is a diffuse hepatic process characterised by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis represents the final histological pathway for a wide variety of liver diseases. The progression to cirrhosis is very variable and may occur over weeks or many years **(Heidelbaugh et al., 2006).**

The main causes are infection with hepatitis C, B viruses, alcohol misuse, and, increasingly, non-alcoholic liver disease; Mostly chronic liver disease is notoriously asymptomatic until cirrhosis with clinical decompensation occurs. Decompensating events include ascites, sepsis, variceal bleeding, encephalopathy, and non-obstructive jaundice **(Samonakis D et al., 2006).**

Ascites, oesophageal varices and bleeding, bacterial peritonitis, hepatorenal syndrome,encephalopathy and hepatocellular carcinoma are common complications of

cirrhosis, Portal hypertension, rather than hepatocyte failure per se, is the underlying cause of most of the complications of cirrhosis and subsequent mortality **(Burroughs et al., 2010).**

From these complications oesophageal varices which are enlarged submucosal veins in the lower part of oesophagus if rupture oesophageal bleeding occurs which is a life thereatening condition and immediate intervention is recommended.

During acute bleeding other organs may be affected like kidney. Acute kidney injury(AKI) in patients with cirrhosis is common and deadly, Up to 20% of hospitalized patients with cirrhosis develop AKI ,and once AKI occurs there is arepeated fourfold increased risk of mortality. In cirrhosis, AKI types include prerenal azotaemia, hepatorenal syndrome (HRS) and interinsic AKI (iAKI) but there effect on mortality risk varies **(Elizabeth C. Verna and Robert S. Brown et al., 2012).**

There is an urgent need for early predictive biomarkers of acute kidney injury (AKI), in this situation early intervention can significantly improve the prognosis. However, currently available biomarkers (such as serum creatinine concentrations) are fraught with imprecision, and their delayed response has impaired our ability to institute potentially effective therapies in a timely manner. Fortunately, the application of innovative technologies has

identified candidates that are emerging as early biomarkers of AKI and CKD. The current status of one of the most promising novel biomarkers, namely neutrophil gelatinase-associated lipocalin (NGAL) **(Nash K et al., 2002)**.

Human NGAL is a 25 kDa protein firstly identified bound to gelatinase in specific granules of the neutrophil. NGAL is a critical component of innate immunity to bacterial infection and is expressed by immune cells, hepatocytes, and renal tubular cells in various disease states ,Its resistance to proteolysis further enhanced potential suitability as a clinical biomarker. It is synthesized and secreted by tubular epithelial cells of the proximal and distal segment. It is freely filtered by the glomerulus, undergoing rapid clearance by the proximal tubule via receptor binding and endocytosis. In healthy kidneys, it is barely detectable in either plasma or urine. However, in the setting of acute tubular injury, NGAL undergoes rapid and profound upregulation with large increases in both urine and plasma. Distinct from traditional markers of function such as creatinine, this rapid response enables NGAL to potentially identify injured kidney much earlier than was previously possible **(Mishra, Mcllory et al., 2010)**.

Aim of the Study

The aim of this work is to monitor serum NGAL (neutrophil gelatinase associated lipocalin) in patients with acute variceal bleeding in liver cirrhotic patients and after recovery during hospital stay and try to correlate with their outcome.

Liver Cirrhosis

Introduction:

Liver weighs approximately 3 pounds and is the largest organ in the body. It is located in the upper right side of the abdomen, behind the lower ribs. When chronic diseases cause the liver to become permanently injured and scarred, the condition is called cirrhosis.**(John I. Allen et al., 2007).**

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture.This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma.**(Schuppan D et al., 2008).**

Lately, this perception has been challenged, because 1-year mortality in cirrhosis varies widely, from 1% to 57%, depending on the occurrence of clinical decompensating events. Histopathologists have proposed that the histological term cirrhosis should be substituted by advanced liver disease, to underline the dynamic processes and variable prognosis of the disorder. Moreover, fibrosis, even in the cirrhotic range, regresses with specific therapy if available, such as antiviral treatment for chronic hepatitis B5 or C **.(Marcellin P et al., 2013)**

Here, we review the current understanding of cirrhosis as a dynamic process and outline current therapeutic options for prevention and treatment of complications of cirrhosis, on the basis of the subclassification in clinical prognostic stages. The new concept in management of patients with cirrhosis is the use of non-specific therapies for prevention and early intervention to stabilise disease progression and to avoid or delay decompensation and the need for liver transplantation.**(Garcia-Tsao G et al 2010)**

Epidemiology

Cirrhosis is an increasing cause of morbidity and mortality in more developed countries. It is the 14th most common cause of death in adults worldwide but the fourth in central Europe; it results in 1·03 million deaths per year worldwide ,170 000 deathes in Euroupe and 33 539 deathes in United states **(Lozano R and Hoyert D et al., 2012).**

Cirrhosis is the main cause indication for 5500 liver transplants each year in Europe. The main causes in more developed countries are infection with hepatitis C virus, alcohol misuse, and, increasingly, non-alcoholic liver disease; infection with hepatitis B virus is the most common cause in sub- Saharan Africa and most parts of Asia. The prevalence of cirrhosis is difficult to assess and probably higher than reported, because the initial stages are asymptomatic so the disorder is undiagnosed. Prevalence was estimated at 0·3% in a French screening programme, and the annual incidence was 15·3–132·6 per 100 000 people in studies in the UK and Sweden**.(Blachier M et al., 2013)**.

Etiology

Causes of cirrhosis

A number of chronic liver diseases can lead to cirrhosis. The cirrhotic process can take from weeks to many years to develop, depending on the underlying cause and other factors, including patient response to the disease process. For example, chronic hepatitis C infection can take up to 40 years to progress to cirrhosis in some people **(Heidelbaugh et al., 2006).**

- Common causes of cirrhosis include:
    - Alcohol abuse.
    - Hepatitis B infection.
    - Hepatitis C infection (up to 20% can develop cirrhosis).
    - Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) (up to 10% of patients with NASH can develop cirrhosis)
- Less common causes include:
    - Haemochromatosis.
    - Primary biliary cirrhosis.

- Biliary obstruction (may be due to biliary atresia/neonatal hepatitis, congenital biliary cysts or cystic fibrosis).
- Autoimmune hepatitis.
- Inherited metabolic disorders, egtyrosinaemia, Wilson's disease, porphyria, alpha-1-antitrypsin deficiency, glycogen storage diseases.
- Sarcoidosis or other granulomatous disease.
- Primary sclerosing cholangitis.
- Venous outflow obstruction in Budd-Chiari syndrome or veno-occlusive disease
- Drugs and toxins including methotrexate, amiodarone and isoniazid.
- Congestive heart failure or tricuspid regurgitation (although this is rarely seen now due to improved management).
- Infections including congenital and tertiary syphilis and schistosomiasis **(Heidelbaugh et al., 2006)**

Pathophysiology

The transition from chronic liver disease to cirrhosis involves inflammation, activation of hepatic stellate cells with ensuing fibrogenesis, angiogenesis, and parenchymal extinction lesions caused by vascular occlusion. This process leads to pronounced hepatic microvascular changes, characterised by sinusoidal remodelling (extracellular matrix deposition from proliferating activated stellate cells resulting in capillarisation of hepatic sinusoids), formation of intra hepatic shunts (due to angiogenesis and loss of parenchymal cells), and hepatic endothelial dysfunction **(Fernandez M et al 2009).**

The endothelial dysfunction is characterised by insufficient release of vasodilators, of which the most important is nitric oxide. Release of nitric oxide is inhibited by low activity of endothelial nitric oxide synthetase (as a result of insufficient protein-kinase-B-dependent phosphorylation, lack of cofactors, increased scavenging resulting from oxidative stress, and high concentrations of endogenous inhibitors of nitric oxide), with concomitant increased production of vasoconstrictors (mainly adrenergic stimulation and thromboxane A2, but also activation of the renin-angiotensin system, antidiuretic hormone, and endothelins).**(Garcia pagan et al., 2012).**

Increased hepatic resistance to portal blood flow is the primary factor increasing portal pressure in cirrhosis (figure 1). It results from the combination of structural disturbances associated with advanced liver disease (accounting for about 70% of total hepatic vascular resistance) and of functional abnormalities leading to endothelial dysfunction and increased hepatic vascular tone; portal pressure could perhaps therefore be decreased by 30% if this functional abnormality were antagonised. The molecular mechanisms of these abnormalities are being delineated and represent new targets for therapy. Splanchnic vasodilation with an ensuing increase in the inflow of blood into the portal venous system contributes to aggravate the increase in portal pressure. Splanchnic vasodilation is an adaptive response to the changes in intrahepatic haemodynamics in cirrhosis; its mechanisms are directly opposite to those of the increased hepatic vascular tone. Because of this opposition, attempts to correct portal hypertension by acting on hepatic resistance or portal blood inflow should be ideally based on strategies acting as selectively as possible on the intrahepatic or the splanchnic circulation. **(Wanless IR et al., 1995)**

In advanced cirrhosis, splanchnic vasodilation is so intense as to determine a hyper dynamic splanchnic and systemic circulation, which together with portal hypertension has a major role in the pathogenesis of ascites and hepatorenal syndrome. Systemic vasodilation further

causes pulmonary ventilation/perfusion mis match that in severe cases leads to hepatopulmonary syndrome and arterial hypoxaemia. Portopulmonary hypertension ischaracterised by pulmonary vaso constriction, which is thought to be due to endothelial dysfunction in the pulmonary circulation. Formation and increase in size of varices is driven by anatomical factors, increased portal pressure and collateral blood flow, and by angiogenesis dependent on vascular endothelial growth factor, all of which contribute to variceal bleeding. Dilation of gastric mucosal vessels leads to portalhypertensive gastropathy. In addition, the shunting of portal blood to the systemic circulation through the portosystemic collaterals is a major determinant of hepatic encephalopathy, of decreased first-pass effect of orally administered drugs, and of decreased reticuloendothelial system function. However, capillarisation of sinusoids and intrahepatic shunts are also important because these changes interfere with effective hepatocyte perfusion, which is a major determinant of liver failure**.(Garcia pagan et al 2012)**

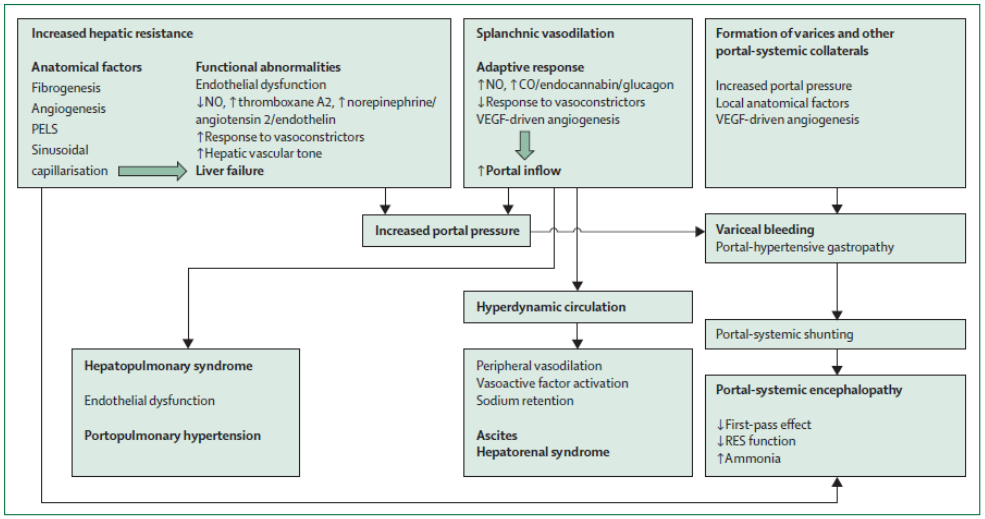

Figure (1): Pathophysiology of portal hypertension in cirrhosis.

PELS=parenchymal extinction lesions.

NO=nitric oxide.

CO=carbon monoxide.

VEGF=vascular endothelial growth factor.

RES=reticuloendothelial system.

Natural course

Cirrhosis should no longer be regarded as a terminal disease and the concept of a dynamic process is increasingly accepted. A prognostic clinical subclassification with four distinct stages has been proposed with substantially differing likelihoods of mortality: stage **1** (compensated with no oesophageal varices) has an estimated mortality of 1% per year, stage **2** (compensated with varices), stage **3** (decompensated with ascites), and **4** (decompensated with gastrointestinal bleeding) have annual mortality rates of 3·4%, 20%, and 57%, respectively.Infections and renal failure have been considered as stage **5**, with 67% 1-year mortality.**(ArvanitiV,Fede G et al., 2010,2012)**

Acute decompensating events that lead to organ failure have mortality of 30%; notably, mortality is higher in previous compensated patients than in those with previous decompensation, which suggests greater tolerance of the latter through the effects of the inflammatory response. Decompensating events are generally triggered by precipitating factors that include infection, portal-vein thrombosis, surgery, and hepatocellular carcinoma **(Fede G et al., 2012)**

Lifestyle changes and general measures

Lifestyle changes tend to be overlooked in the management of cirrhosis, because life expectancy is judged to be short and the benefit is difficult to measure. Although evidence comes from cohort or case-control studies, lifestyle advice should still be offered to all patients, because it is easily implemented with little risk of side-effects or cost. Insulin resistance, obesity, and the metabolic syndrome are pathophysiologically linked with nonalcoholic fatty liver disease, but they have deleterious effects irrespective of liver disease aetiology. Obesity is an independent predictor of cirrhosis in alcoholic liver disease ,and the presence of metabolic syndrome is associated with more severe fibrosis and cirrhosis in chronic liver disease**.(Tsochatzis E et al., 2008)**

In 161 patients with compensated cirrhosis who were followed up prospectively, obesity was independently associated with clinical decompensation,together with HVPG and serum albumin**.(Berzigotti A et al., 2011)** Moreover, insulin resistance and metabolic syndrome were independently associated with liver relate mortality in a NHANES-III cohort of more than 2500 patients with chronic liver disease.Insulin resistance predicts the