INTRODUCTION

Chronic liver diseases and their complications constitute a major health problem all over the world and especially in Egypt ***(Aref et al., 2004).*** Most of the morbidity and mortality of chronic liver diseases is due to its progression to cirrhosis and complications of cirrhosis ***(Runyon, 2004).***

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, have resulted in improved management, quality of life, and life expectancy of patients ***(Schuppan and Afdhal, 2008)***.

Major complications of chronic liver diseases include (varices, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, portal hypertension, Hepatic encephalopathy and thrombocytopenia) ***(Aref et al., 2004).***

Ascites is the most common major complication of cirrhosis. When liver damage progresses to an advanced stage, signals are sent to the kidneys to retain salt and water in the body with fluid collection in the legs and in the abdominal cavity between the abdominal wall and the abdominal organs (ascites) ***(Runyon, 2004).***

Hepatocellular carcinoma (HCC) is generally occurring in association with cirrhosis, particularly due to hepatitis C, hepatitis B, alcohol, hereditary hemochromatosis, and primary biliary cirrhosis ***(Bruix and Sherman, 2005).***

Approximately 80% of HCC cases arise in developing countries. In Egypt, there is a rising trend of HCC as there was nearly a two fold increase of the proportion of HCC among chronic liver disease patients over the last decade ***(El-Zayadi et al., 2005).***

Cancer antigen 125 ***(CA 125)*** is a high-molecular-weight glycoprotein identified by murine monoclonal antibody against epithelial ovarian cancer ***(Bast et al., 1981).*** Serum ***CA 125*** levels are increased in patients with epithelial ovarian cancer and thus may be used to monitor disease progression or assess the effects of therapy in such patients ***(Rustin et al., 1996)***. However, the specificity of elevated ***CA 125*** levels is low. Elevated levels have been recognized in physiologic conditions such as menstruation ***(Lehtoverta et al., 1990)*** and pathological conditions such as non-ovarian abdominal malignancies ***(Haga et al., 1986).*** Although high ***CA125*** levels are detected in patients with liver disease ***(Molina et al., 1991 and Zuckerman et al., 1995),*** this phenomenon is not widely appreciated.

Thus, an elevation in ***CA 125*** in perimenopausal women with ascites secondary to cirrhosis often leads to the mistaken diagnosis of ovarian cancer, and such patients may even undergo subsequent surgery ***(Dibaise and Donoval, 1999).***

In chronic liver diseases, especially liver cirrhosis, ***CA125*** levels are usually elevated. In acute and chronic hepatitis, this rate is 2-22%, and in cirrhosis 20-100% ***(Jalanko et al., 1985 and Eerdekends et al., 1985).*** The elevation of serum ***CA 125*** is common in liver cirrhosis patients.

It is correlated with the amount of ascites, and possibly the insufficiency of liver function ***(WEN-BIN and YU-LAN, 2003).*** ***CA125*** and AFP are commonly measured in the laboratory for their value as HCC markers. The Sensitivities for ***CA 125*** in HCC have been reported to range from 43% to more than 90%. However, the specificity of ***CA125*** in relation to benign liver diseases was poor ***(Elias and Kew, 1990 and Lopez et al., 1996).*** **T**ogether, AFP (cut-off: 200 ng/mL) and ***CA 125*** have been reported to give a combined sensitivity of 96%. The use of AFP (sensitivity 58.8%, specificity of 97.4%) and ***CA125*** (sensitivity of 92%, specificity 48.5%) together as screening blood markers for HCC has been suggested, a negative result for both markers would most likely rule out HCC ***(Lopez et al., 1996).*** Despite its excellent sensitivity for HCC, it should be noted that raised ***CA125*** occurs in both benign and malignant liver disease. It is closely associated with the presence of ascites and is especially elevated when this condition is present ***(Bergmann et al., 1986 and Devarbhavi et al., 2002).***

AIM OF THE WORK

The aims of the work are:

1. To determine the association between elevated levels of serum cancer antigen ***(CA125)*** and progression of liver disease.
2. To explore the association between serum level of ***CA125*** in decompensated post-hepatitic HCV cirrhosis with ascites.
3. To assess the serum level of ***CA125*** in hepatocellular carcinoma.

Chapter1

LIVER CIRRHOSIS

Introduction:

Cirrhosis is defined as the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, which leads to portal hypertension and end-stage liver disease. Recent advances in the understanding of the natural history and pathophysiology of cirrhosis, and in treatment of its complications, have resulted in improved management, quality of life, and life expectancy of patients. Liver transplantation remains the only curative option for a selected group of patients, but pharmacological treatments that can halt progression to decompensated cirrhosis or even reverse cirrhosis are currently being developed ***(Schuppan and Afdhal, 2008).***

Approximately 40 percent of patients with cirrhosis are asymptomatic, and the condition often is discovered during a routine examination with laboratory or radiographic studies, or at autopsy ***(National Center for Health Statistics, 2006).***

In most persons, approximately 80 to 90 percent of the liver parenchyma must be destroyed before liver failure is manifested clinically. When complications of cirrhosis occur, they typically are related to impaired hepatic function or actual

physical disruption and reorganization of the liver parenchyma ***(Friedman and Schiano, 2004).***

Pathogenesis and pathophysiology of cirrhosis

Fibrosis describes encapsulation or replacement of injured tissue by a collagenous scar. Liver fibrosis results from the perpetuation of the normal wound healing response resulting in an abnormal continuation of fibrogenesis (connective tissue production and deposition). Fibrosis progresses at variable rates depending on the cause of liver disease, environmental and host factors ***(Schiff et al., 2003).*** Cirrhosis is an advanced stage of liver fibrosis that is accompanied by distortion of the hepatic vasculature. It leads to shunting of the portal and arterial blood supply directly into the hepatic outflow (central veins), compromising exchange between hepatic sinusoids and the adjacent liver parenchyma, i.e., hepatocytes. The hepatic sinusoids are lined by fenestrated endothelia which rest on a sheet of permeable connective tissue (the space of Disse) which contains hepatic stellate cells (HSC) and some mononuclear cells. The other side of the space of Disse is lined by hepatocytes which execute most of the known liver functions. In cirrhosis the space of Disse is filled with scar tissue and endothelial fenestrations are lost, a process termed sinusoidal capillarization ***(Schaffner and Popper, 1963).*** Histologically, cirrhosis is characterized by vascularized fibrotic septa that link portal tracts with each other and with central veins, leading to hepatocyte islands that are surrounded

by fibrotic septa and which are devoid of a central vein **(Figure1)**.

Molecular pathology of hepatic fibrosis and cirrhosis:

The scar tissue in cirrhosis is composed of a complex assembly of different extracellular matrix (ECM) molecules, comprising the fibril forming interstitial collagens type I and III, basement membrane collagen type IV, noncollagenous glycoproteins like fibronectin and laminin, elastic fibers and glycosaminoglycans and proteoglycans among others ***(Schuppan et al., 2001).***

Toxins, viruses, cholestasis, or hypoxia can trigger a wound healing reaction termed fibrogenesis, i.e., the excess synthesis and deposition of ECM. Initially, fibrogenesis is counterbalanced by removal of excess ECM by proteolytic enzymes, such as certain matrix metalloproteinases (MMPs) ***(Benyon and Arthur, 2001).***

Chronic damage usually favours fibrogenesis over fibrolysis, with an upregulation of tissue inhibitors of MMPs (TIMPs) ***(Riordan and Williams, 2006).*** The major hepatic ECM producing cells are myofibroblasts that either derive from activated hepatic stellate cells (HSC) or perivascular fibroblasts ***(Friedman, 2000; Knittel et al., 1999 and Schuppan et al., 2003).*** Myofibroblast activation is mainly driven via fibrogenic cytokines and growth factors that are released by activated macrophages (Kupffer cells), other inflammatory cells and bile

duct epithelia. The most prominent profibrogenic cytokine is transforming growth factor β which suppresses inflammation, but drives fibrogenic gene expression in these Myofibroblasts ***(Friedman, 2000; Schuppan et al., 2003 and Bissell et al., 2001).***

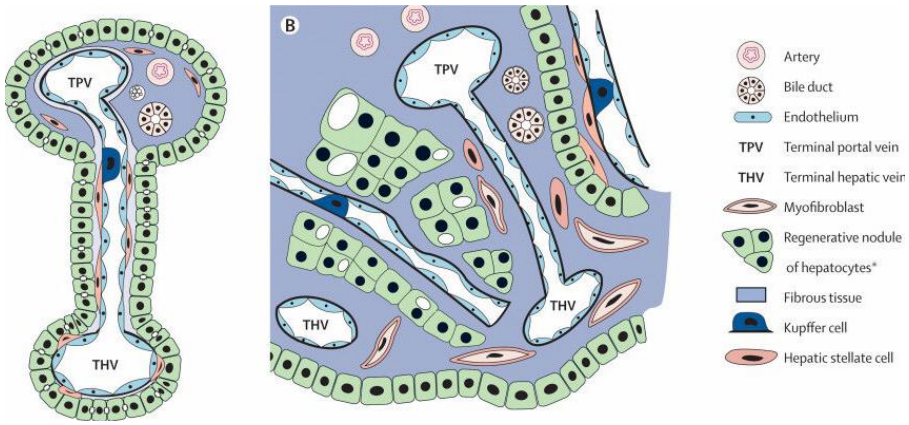

Figure (1): Vascular and architectural alterations in cirrhosis ***(Schuppan and Afdhal, 2008)***

Mesenteric blood flows via the portal vein and the hepatic artery that extend branches into terminal portal tracts.

A) Normal liver: Terminal portal tract blood runs through the hepatic sinusoids where fenestrated sinusoidal endothelium which rest on loose connective tissue (space of Disse') allow for extensive metabolic exchange with the lobular hepatocytes; sinusoidal blood is collected by terminal hepatic venules which disembogue into one of the 3 hepatic veins and finally the caval vein.

B) Cirrhosis: Activated myofibroblasts that derive from perisinusoidal hepatic stellate cells and portal or central vein fibroblasts proliferate and produce excess

extracellular matrix (ECM). This leads to fibrous portal tract expansion, central vein fibrosis and capillarization of the sinusoids, characterized by loss of endothelial fenestrations, congestion of the space of Disse' with ECM, and separation/encasement of perisinusoidal hepatocyte islands from sinusoidal blood flow by collagenous septa. Blood is directly shunted from terminal portal veins and arteries to central veins, with consequent (intrahepatic) portal hypertension and compromised liver synthetic function ***(Schuppan and Afdhal, 2008).***

The major clinical consequences of cirrhosis are impaired hepatocyte (liver) function, an increased intrahepatic resistance (portal hypertension) and the development of hepatocellular carcinoma (HCC). The general circulatory abnormalities in cirrhosis (splanchnic vasodilation, vasoconstriction and hypoperfusion of kidneys, water and salt retention, increased cardiac output) are intimately linked to the hepatic vascular alterations and the resulting portal hypertension. Cirrhosis and its associated vascular distortion are traditionally considered to be irreversible but recent data suggest that cirrhosis regression or even reversal is possible ***(Desmet and Roskams, 2004).***

Etiology of liver cirrhosis:

It is important to know the etiology of cirrhosis, since it can predict complications and direct treatment decisions. It also allows the discussion of preventive measures, e.g., with family

members of patients with alcoholic cirrhosis or chronic viral hepatitis, and consideration of (genetic) testing and preventive advice for relatives of patients with genetic diseases, such as hemochromatosis or Wilson's disease ***(Schuppan and Afdhal, 2008).***

Cirrhosis can be caused by many things some known and others unknown:

1) *Alcohol*: Using alcohol in excess is the most common cause of cirrhosis in the United States (60 to 70 percent) ***(Schuppan and Afdhal, 2008).***

2) *nonalcoholic steatohepatitis (NASH):* older age obesity, insulin resistance/type 2 diabetes, hypertension and hyperlipidemia (all features of the metabolic syndrome) lead to NASH ***(Clark, 2006 and Farrell and Larter, 2006).***

3) *Chronic Viral Hepatitis*: Type B and Type C hepatitis, and perhaps other viruses, can infect and damage the liver over a prolonged time and eventually cause cirrhosis. Hepatitis B and C transmission may be due to birth place in endemic areas, sexual history exposure risk, intranasal or intravenous drug use, body piercing or tattooing, accidental contamination with blood or body fluids as well as blood transfusion history ***(Friedman and Schiano, 2004).***

4) *Chronic Bile Duct Blockage*: This condition can occur at birth (biliary atresia) or develop later in life (primary biliary cirrhosis). The cause of the latter remains unknown. When the bile ducts outside the liver become narrowed and blocked, the condition is called primary sclerosing cholangitis. This condition is often associated with chronic ulceration of the colon (colitis).

5) *Abnormal Storage of Copper (Wilson's disease) or Iron (Hemochromatosis):* These metals are present in all body cells. When abnormal amounts of them accumulate in the liver, scarring and cirrhosis may develop. ***(Schuppan and Afdhal, 2008)***

6) *Drugs and Toxins:* Prolonged exposure to certain chemicals or drugs can scar the liver like:

- Alpha-methyldopa
- Amiodarone
- Isoniazid
- Methotrexate
- Oxyphenisatin
- Perhexiline
- Troglitazone
- Vitamin A

(Friedman and Schiano, 2004)

7) *Autoimmune Hepatitis:* This chronic inflammation occurs when the body's protective antibodies fail to recognize the liver as its own tissue. The antibodies injure the liver cells as though they were a foreign protein or bacteria.

8) Cystic Fibrosis and Alpha l-antitrypsin Deficiency: These disorders are inherited ***(Schuppan and Afdhal, 2008).***

9) *Other causes of liver cirrhosis* are:

- Infection like; Schistosomiasis, Brucellosis, Congenital or tertiary syphilis and Echinococcosis.
- Vascular abnormalities like; Chronic, passive hepatic congestion caused by right-sided heart failure, pericarditis, Budd-Chiari syndrome, Veno-occlusive disease and Hereditary hemorrhagic telangiectasia (Osler-Weber- Rendu disease)
- Idiopathic/miscellaneous like; Granulomatous liver disease (e.g., sarcoidosis), Idiopathic portal fibrosis, Polycystic liver disease and Indian childhood cirrhosis.

(Friedman and Schiano, 2004)

Clinical presentation of cirrhosis:

History:

Most of the morbidity and mortality of chronic liver diseases is due to its progression to cirrhosis and complications of cirrhosis ***(Schuppan and Afdhal, 2008).***

Cirrhosis is the end-stage of every chronic liver disease. Its natural history is characterized by an asymptomatic phase, termed 'compensated' cirrhosis or may be manifest as anorexia and weight loss, weakness, fatigue, and even osteoporosis as a result of vitamin D malabsorption and subsequent calcium deficiency ***(Heidelbaugh and Sherbondy, 2006).*** The compensated cirrhosis followed by a rapidly progressive phase marked by the development of complications of portal hypertension and/or liver dysfunction, termed 'decompensated cirrhosis'. In the compensated phase, portal pressure may be normal or below the threshold level identified for the development of varices or ascites (clinically significant portal hypertension) ***(D'Amico et al., 2001).***

As the disease progresses, portal pressure increases and liver function decreases, resulting in the development of ascites, portal hypertensive gastrointestinal (GI) bleeding, encephalopathy and jaundice. The development of any of these complications marks the transition from a compensated to a decompensated phase. Progression may be accelerated by the development of other complications such as (re)bleeding, renal

impairment (refractory ascites, hepatorenal syndrome), hepatopulmonary syndrome, spontaneous bacterial peritonitis. The development of hepatocellular carcinoma (HCC) may accelerate the course of the disease at any stage ***(D'Amico et al., 2006).***

Classification of cirrhosis into a compensated and a decompensated stage is simple and reproducible and identifies patients at a similar rate of disease progression and survival. Decompensated cirrhosis is defined by the presence of ascites, variceal bleeding, encephalopathy and/or jaundice ***(Gines et al., 1987).*** Moreover, since ascites is most frequently the first of these signs to appear ***(D'Amico et al., 1986).*** It is usually considered a landmark sign of decompensated cirrhosis. Transition from a compensated to a decompensated stage occurs at a rate of 5–7% per year ***(D'Amico, 2001).***

By combining data from two large natural history studies including 1649 patients ***(D'Amico et al., 1986 and D'Amico et al., 2001),*** four clinical stages or status of cirrhosis can be identified, each with distinct clinical features and a markedly different prognosis. Each stage is defined by the presence or absence of complications of cirrhosis and was agreed upon in the recent Baveno IV consensus conference ***(de Franchis, 2005).***

Stage 1 is characterized by the absence of esophageal varices and of ascites. While patients remain in this status, the mortality rate is as low as 1% per year. Patients exit this status

at a cumulative rate of 11.4% per year: 7% because of the development of varices and 4.4% because of the development of ascites (with or without varices).

Stage 2 is characterized by the presence of esophageal varices without ascites and without bleeding. While patients remain in this status, the mortality rate is 3.4% per year. Patients leave this status by developing ascites (6.6% per year) or by developing variceal bleeding before or at the time of development of ascites (rate 4% per year).

Stage 3 is characterized by ascites with or without esophageal varices in a patient that has never bled. While patients remain in this status, the mortality rate is 20% per year, significantly higher than in the two former states. Patients exit this stage by bleeding (7.6% per year).

Stage 4 is characterized by GI bleeding with or without ascites. In this stage the one-year mortality rate is 57% (nearly half of these deaths occur within 6 weeks from the initial episode of bleeding).

Stages 1 and 2 correspond to patients with compensated cirrhosis while *stages 3 and 4* refer to decompensated cirrhosis. HCC develops at a fairly constant rate of 3% per year and is associated with a worse outcome at whatever status it develops.

In the aforementioned consensus conference on portal hypertension it was suggested that this status classification