INTRODUCTION

Chronic liver diseases represent an important public health problem.Infections with Hepatitis B or C viruses,non alcoholic fatty liver disease represent the majority of the liver diseases,the rest of them (genetic, autoimmune or metabolic) have a minor contribution.Hepatic fibrosis represents the cicatriceal response to the chronic injury, regardless of the cause.Cirrhosis is the main long term complication of chronic hepatopathies ***(Riley and Bhatti, 2001).***

Accurate estimation of the chronic liver disease severity is helpful for the evaluation of the therapeutic effect and the prognosis of the disease. At present, there are 3 ways for this purpose, namely histology, serology and imaging ***(Zheng et al., 2003).***

Liver biopsy is the gold standard for diagnosis and assessment of fibrosis and necroinflammatory changes in chronic hepatitis and cirrhosis, however the use of biopsy in clinical practice has some limitations related to sample errors and difficulty in being repeated during follow up ***(Nord, 1982).*** Also it is sometimes difficult to be accepted by the patients because of its invasiveness and also possible side effects (pain in 1/3 of the patients and severe complications in 0.3 % of the patients) Moreover, the diagnostic value of hepatic biopsy is limited by sampling variability, the average size of the prelevaled fragment is

15 mm, which represents 1/50,000 of the entire organ ***(Ghany and Doo, 2005 and Kelleher and Afdhal, 2005).***

In addition it is well known that liver parenchymal damage in chronic hepatitis and cirrhosis in not uniform thus sample errors are commonly encountered ***(Zheng et al., 2003).***

The non invasive assessment of chronic liver disease has been attempted by various research groups comprising either clinical signs ***(Wells, 1999 and Kelleher and Afdhal, 2005)*** gray scale ***(Tanaka et al, 1995)*** and colour Doppler Ultrasound signs and indices ***(Chen et al, 2005).***

Ultrasonography has become the most common and valuable method because of its low cost, easy performance and high acceptability by the patients.It could provide not only valuable information on the morphological changes of the liver but also liver hemodynamics by colour Doppler flow imaging **(*Chen et al, 2005).***

Doppler sonography is an important diagnostic modality for evaluating patients with hepatic disease.The hepatic vessels are of large caliber and have sufficient flow to be easily examined by US. In addition, both diffuse and focal diseases of the liver produce dramatic change in the circulatory patterns that are detectable with Colour Doppler. Colour Doppler is also important in assessing vascular complications after liver transplantation and transjagular

intrahepatic portosystemic shunt (TIPS) placement ***(Shapiro et al., 1998).***

AIM OF THE WORK

To evaluate the relationship between abdominal ultrasonography and selected colour Doppler parameters on one hand and the liver histopathology on the other hand, in patients with chronic liver disease.

CHRONIC LIVER DISEASE

Chronic liver disease is marked by the gradual destruction of liver tissue over time. Several liver diseases fall under this category, including: Cirrhosis of the liver and Fibrosis of the liver. Cirrhosis represents the final common histologic pathway for a wide variety of chronic liver diseases. The term cirrhosis was first introduced by Laennec in 1826. It is derived from the Greek term *scirrhus* and is used to describe the orange or tawny surface of the liver seen at autopsy ***(Wolf, 2008).***

Causes of chronic liver disease and cirrhosis

Viral Hepatitis, Autoimmune hepatitis, Primary biliary cirrhosis, Secondary biliary cirrhosis (associated with chronic extrahepatic bile duct obstruction), Primary sclerosing cholangitis, Hemochromatosis, Wilson‘s disease, Alpha-1 antitrypsin deficiency, Granulomatous disease (eg, sarcoidosis) , Type IV glycogen storage disease, Drug-induced liver disease (eg, methotrexate, alpha methyldopa, amiodarone), Venous outflow obstruction (eg, Budd-Chiari syndrome, veno-occlusive disease), Chronic right-sided heart failure, Tricuspid regurgitation and Aphla toxins ***(Wolf, 2008).***

I. Viral hepatitis

With the advances in novel technologies, eight distinct types of hepatitis virus have been described: Hepatitis A, B, C, D, E, G, TT and SEN viruses ***(Poovorawan et al., 2002).***

Hepatitis A and E viruses are transmitted by the fecal-oral route and do not induce a chronic carrier state. Parenterally transmitted hepatitis B and C viruses are major causes of chronic liver disease, including cirrhosis, hepatocellular carcinoma and end-stage liver failure. Hepatitis D virus is unable to replicate on its own, it requires an established hepatitis B virus infection to be able to replicate. Hepatitis G and TT viruses have been characterized within the latter part of the past decade but their significance as to the cause of human liver disease has yet to be elucidated. Likewise, the precise impact of the most recently described SEN virus isolated from patients with post-transfusion hepatitis awaits further studies ***(Poovorawan et al., 2002).***

1. Hepatitis C virus (HCV)

Scope of hepatitis C problem

The hepatitis C virus (HCV) is one of the most significant health problems affecting the liver. More than 4 million Americans (1.3% of the U.S. population) and 170 million individuals in the world (3% worldwide) are infected with hepatitis C virus ***(Fong, 2008).***

Epidemiology

The prevelance in Egypt is over 20% and it is the most common cause of chronic liver disease ***(Habib et al., 2001).*** Children and young adults have relatively high anti HCV prevalence ***(Medhat et al., 2002).***

In Egypt the genotype 4 is extremely variable, not only in terms of sequence, but also in terms of functional and immunological determinants. These data should be taken into account in planning the development of vaccine trials in Egypt ***(Genovese et al., 2005).***

The timing and the speed of spread provide evidance that the Egyptian HCV epidemic was initiated and propagated by extensive antischistosomiasis injection campaigns ***(Pybus et al., 2003).***

In blood donors antibody prevelance ranged from 6 % up to 38% with an average of 15 %.This high prevelance of HCV in the general population suggests a differance in the transmission and the natural history of HCV in Egypt compared with the United States and Europe and other developed and developing countries **(Nafeh et al, 2000).**

Transmission of hepatitis C virus

HCV is transmitted through blood transfusion, IV drug use, occupational exposure (needle stick injury), sexual contact (about 5 %), iatrogenic as in renal dialysis, dentists, acupuncture, interventional surgical or endoscopic and perinatal transmission (uncommon, less than 5%) ***(El-Zayadi et al., 2006).***

Histopathology

Hepatitis C can cause a range of hepatic histopathology.

The virus may cause an acute hepatitis indistinguishable from any other acute viral hepatitis, but it is more likely to be associated with *steatosis, bile duct injury, and portal lymphoid aggregates.* Chronic infection with hepatitis C can range from mild nonspecific changes, presumably representing a hepatitis C carrier state, to end-stage liver disease with cirrhosis and hepatocellular carcinoma. Between these is chronic hepatitis of varying severity. Steatosis, portal lymphoid aggregates, and bile duct injury, while not specific, are very characteristic of chronic hepatitis C. Reputed precursors of hepatocellular carcinoma, including *liver cell dysplasia* and *adenomatous hyperplasia*, frequently follow the development of *cirrhosis* and are presumed to predispose to the development of malignancy ***(Goodman and Ishak, 1995).***

Fate of HCV infection

One of the major problems with hepatitis C virus infections is that 85% of individuals initially infected with this virus will become chronically infected, usually for decades. The other 15% of hepatitis C virus infected individuals simply have an acute infection; that is, one that resolves spontaneously in a few weeks or months. The propensity of hepatitis C virus to cause chronic infection is explained by the extraordinary ability of this virus (in contrast to most other viruses, including hepatitis A) to avoid destruction by the body's immune defense system and its persistence in the mononuclear cells ***(Fong, 2008).***

Once established, chronic hepatitis C virus infection causes an inflammation of the liver called chronic hepatitis. This condition can progress to scarring of the liver, which is called fibrosis, or more advanced scarring, which is called cirrhosis in 20 % of the cases within 10 to 20 years; HCC develops in approximately 5% of the cirrhotic patients in 20 to 30 years ***(El - Zayadi et al., 2006).***

In Egypt there are many comorbid factors that lead to alteration of the natural history of HCV, thus leading to more inflammation and a higher rate of progression of liver disease.These factors include Schistosomiasis, hepatitis B infection, fatty liver disease, recurrent exposure to environmental toxins and pesticides. Most of these factors along with cirrhosis increase the risk of HCC ***(El-Zayadi et al., 2006).***

2. Hepatitis B (HBV)

HBV is a Hepadna virus. It is an extremely resistant strain capable of withstanding extreme temperatures and humidity ***(Pyrsopoulos, 2007).***

In 1965, Blumberg et al reported the discovery of the hepatitis B surface antigen (HBsAg), also known as Australia antigen, and its antibody, hepatitis B surface antibody (HBsAb). A few years later, in 1970, Dane visualized the hepatitis B virus (HBV) virion. Since then, considerable progress has been made regarding the epidemiology, virology,

natural history, and treatment of this hepatotropic virus ***(Geramizadeh et al., 2008).***

Hepatitis B is a worldwide health care problem; especially in developing areas.About one third of the world's population has been exposed at some time to the hepatitis B virus (HBV). Moreover, approximately 350 million individuals worldwide are chronically (long duration) infected with this virus. As a result, the complications of hepatitis B viral infection lead to two million deaths annually **(Fong, 2008).** Until now, there are eight known genotypes of HBV (A-H**)** ***(Geramizadeh et al., 2008).***

Transmission

Hepatitis B is transmitted both hematogenously through blood transfusion, needle stick injuries, renal dialysis and sexually also vertical transmission may occur ***(Pyrsopoulos, 2007)***.

Pathogenesis

The pathogenesis and clinical manifestations are due to the interaction of the virus and the host immune system. The latter attacks the HBV and causes liver injury. Activated $CD4^+$ and $CD8^+$ lymphocytes recognize various HBV-derived peptides located on the surface of the hepatocytes, and an immunologic reaction occurs. Impaired immune reactions (eg, cytokine release, antibody production) or relatively tolerant immune status results in chronic hepatitis.In particular, a

restricted T cell–mediated lymphocytic response occurs against the HBV-infected hepatocytes.

The final state of the disease is cirrhosis. Patients with cirrhosis and HBV infection are likely to develop HCC ***(Pyrsopoulos, 2007).***

Histopathology

HBV infection may generate ground-glass hepatocytes, with a finely granular, eosinophilic cytoplasm depicted as spheres and tubules of HBsAg using electron microscopy. Other HBV-infected hepatocytes may have sanded nuclei due to abundant HBcAg; this finding indicates active viral replication ***(Sharma, 2008).***

With **acute hepatitis**, hepatocyte injury takes the form of diffuse swelling *(balloon degeneration*). *Cholestasis* is an inconstant finding. Two patterns of hepatocyte cell death are observed*: cytolysis* (cell rupture) and *apoptosis* (cell shrinkage). In severe cases, *confluent necrosis* of hepatocytes may lead to *bridging necrosis*. Inflammation is a prominent feature of acute hepatitis. Kupffer cells undergo hypertrophy and hyperplasia. Usually, the portal tracts are infiltrated with a mixture of inflammatory cells. Histologic features of **chronic hepatitis** range from exceedingly mild to severe. In the mildest forms, significant inflammation is limited to the portal tracts. Liver architecture is usually well preserved, but smoldering hepatocyte necrosis throughout the lobule may occur in all

forms of chronic hepatitis. Continued *interface hepatitis* and bridging necrosis are harbingers of progressive liver damage. Deposition of fibrous tissue is the hallmark of irreversible liver damage. Continued loss of hepatocytes and fibrosis results in *cirrhosis,* with *fibrous septae* and hepatocyte *regenerative nodules*. This pattern of cirrhosis is characterized by irregularly sized nodules separated by variable, but mostly broad, scars. Historically, this pattern of cirrhosis has been termed postnecrotic cirrhosis. The term postnecrotic cirrhosis has been applied to all forms of cirrhosis in which the liver shows large, irregular-sized nodules with broad scars, regardless of etiology ***(Sharma, 2008).***

3. Hepatitis B virus and Delta virus agent

The delta hepatitis virus (HDV) is an RNA virus, meaning that its genetic material is made up of ribonucleic acid. It is a small virus that requires the hepatitis B virus to survive. HDV cannot survive on its own because it requires the hepatitis B virus envelope (HBsAg) to enable it to infect the liver cells ***(Fong, 2008).***

Transmission

The ways in which HDV is transmitted are, by exposure to contaminated blood, especially intravenous drug use, and by sexual contact, which are essentially the same as for hepatitis B virus ***(Fong, 2008).***

Acute hepatitis B virus and acute delta hepatitis can be acquired at the same time, which results in a more severe form of acute hepatitis. Most of these patients, however, will subsequently clear both the hepatitis B virus and delta hepatitis virus. Individuals who already have chronic hepatitis B also can acquire acute delta hepatitis. These individuals, however, usually will go on to develop chronic delta hepatitis infection on top of their chronic hepatitis B infection. Furthermore, individuals who have chronic delta hepatitis infection (and, by definition, chronic hepatitis B viral infection) will almost always develop cirrhosis (severe liver scarring) rapidly.Chronic delta hepatitis with chronic hepatitis B virus co-infection is very difficult to treat. These patients require at least one year of interferon therapy. Still, most treated patients will have a relapse after interferon is discontinued. Furthermore, lamivudine has no effect on the delta hepatitis virus ***(Fong, 2008).***

4. Hepatitis E virus

Hepatitis E virus was previously known as enterically transmitted non-A, non-B hepatitis, is a self limiting infectious viral disease of developing countries. Various issues regarding the pathogenesis of liver injury and its natural history remain unanswered after two decades of its discovery. A small proportion of patients develop fulminant hepatic failure. Mortality is very high if it is associated with pregnancy, especially during third trimester ***(Kc et al., 2006).***

After establishment of hepatitis A virus as a cause of decompensation of chronic liver disease.Now there are reports that hepatitis E viruses also does the same. Acute hepatitis E in these patients has a protracted course with high morbidity and mortality. Seroprevalence studies showed that 44% of patients with chronic liver disease were at risk of developing hepatitis E ***(Kc et al., 2006).***

Many patients develop hepatorenal syndrome, hepatic encephalopathy and even liver failure after co-infection with hepatitis E virus. Now time has come to institute hepatitis E virus superinfection as one of the cause of acute on chronic liver failure.Hepatitis E is a problem of developing countries. Sudden decompensation in chronic liver disease patient, who were otherwise stable and under regular follow up, should be carefully dealt with. Patients of chronic liver disease traveling to endemic zone should take precaution. If vaccine against hepatitis E virus is developed, chronic liver disease patient would be the eligible candidate for vaccination beside pregnant ladies ***(Kc et al., 2006).***

Histopathology

Liver biopsy usually is not necessary. The pathology picture is cholestatic, with stasis of canalicular bile and marked proliferation of intralobular bile ductules. The cholestasis is most notable within the centroacinar regions. Parenchymal changes are less severe and include swollen hepatocytes, foam cells, and acidophil bodies. Inflammatory infiltrate of

mononuclear cells is present, resulting in expanded portal areas and possible piecemeal necrosis ***(Schwartz, 2008).***

II. Hepatic steatosis

Non alcoholic fatty liver disease represents a spectrum of liver diseases characterized mainly by macrovesicular steatosis that occurs in the absence of alcoholic consumption. The hepatic histology varies from isolated hepatic steatosis alone "first hit" to fatty liver accompanied by hepatocellular damage plus inflammation known as steatohepatitis "second hit" which is followed by the development of fibrosis. Adipose tissue is now recognized as not simply a storage depot for excess energy, but rather an active endocrine organ that secretes a number of molecules termed, adipocytokines. A number of these adipocytokines have been linked to alterations in insulin sensitivity, including adiponectin, leptin, resistin, and tumor necrosis factor-a (TNF-a) ***(Kern et al., 2001 and Schaffler et al., 2005).***

Definition of steatosis

Hepatic steatosis is caused by imbalance between the delivery of fat in the liver and its subsequent secretion or metabolism. In other words, fat accumulates when the delivery of fatty acids to the liver, either from the circulation or by de novo synthesis within the liver, exceeds that capacity of the liver to metabolize the fat by b-oxidation or secrete it as very low-density lipoproteins (VLDL). Derangements in any of