INTRODUCTION

Chronic liver disease is a disease process of the liver that involves progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. It may be viral, metabolic, autoimmune, drug induced, alcoholic or congenital**.** In Egypt, clinical studies showed that 70-90% of patients with chronic hepatitis and cirrhosis had hepatitis C infection. Co-infection with schistosomiasis causes more severe liver disease than HCV alone alone***(Kamath and Kim, 2007).***

Liver cirrhosis is associated with many cardiovascular changes or abnormalities, including hyperdynamic circulation, hepatopulmonary syndrome, and hepatorenal syndrome (HRS) ***(Sorte et al .,1999).***

Renal dysfunction begins early in cirrhosis even before the patient develops decompensated cirrhosis. This is due to hemodynamic changes associated with imbalance between vasodilators and vasoconstrictors leading to renal vasoconstriction and low renal blood flow ***(Angelie et al., 2006)***.

Hepatorenal syndrome (HRS) is a life-threatening medical condition that consists of rapid deterioration in kidney function in individuals with cirrhosis or fulminant liver failure**.**It is a relatively common complication of cirrhosis, occurring in 18% of cirrhotics within one year of their diagnosis, and in 39% of

cirrhotics within five years of their diagnosis. HRS can affect individuals with cirrhosis (regardless of cause), severe alcoholic hepatitis, or fulminant hepatic failure***(Arroy et al., 1996).***

The important features of HRS are characterized by peripheral vasodilation with subsequent profound intrarenal vasoconstriction, leading to decreased glomerular filtration rate***(Chan et al.,2007).***

Currently, there are 2 distinct types: Type 1 HRS often manifests itself rapidly; without appropriate treatment the mean survival time is approximately 2 weeks ***(Gines et al., 2004).*** In more than 70% of cases there is an identifiable trigger for type 1 HRS. A large number of studies have shown that type 1 HRS can be precipitated by preceding spontaneous bacterial peritonitis infections, gastrointestinal bleeding and large-volume abdominal paracentesis without albumin replacement. Furthermore, type 2 HRS has a gradual onset with a steady decline in renal function. Interestingly, the hallmark for type 2 HRS is refractory ascites and often has no precipitating factors. The survival time is better in type 2 HRS at approximately 6 months***(Salerno et al., 2007).***

Nitric oxide is a vasodilator molecule, produced by an enzyme called nitric oxide synthase (NOS) that converts oxygen and arginine into citrruline and nitric oxide ***(Parvue, 2005)***. The site of Nitric oxide metabolites,nitrate and nitrite (NOx) production is likely the endothelial cells, which express

the bulk of constitutive NOS activity responsible for NO release into the bloodstream**.** Nitric oxide has a very short half-life; therefore, measurement of the (NOx), are commonly used to estimate NO levels in the circulation ***(Coskun et al., 2001).***

Nitric oxide is elevated in patient with cirrhosis, the imbalance between it and vasoconstrictors such as endothelin 1 in the renal microcirculation has been proposed to be responsible for deterioration of kidney function in these patients**.**Moreover, a progressive rise in levels of NOx had been proposed during progressive renal dysfunction in cirrhosis ***(Kayali et al., 2009).***

AIM OF THE WORK

This study aims to:

Correlate between the serum level of Nitric oxide and renal impairment in cirrhotic patients.

LIVER CIRRHOSIS

Chronic liver disease is a disease process of the liver that involves progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis. It may be viral, metabolic, autoimmune, drug induced, alcoholic or congenital ***(Kamath and Kim, 2007).***

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by fibrosis, scar tissue and regenerative nodules (lumps that occur as a result of a process in which damaged tissue is regenerated leading to loss of liver function). Depending upon their size, the defect is termed as "macronodular" (>3 mm in diameter) or "micronodular cirrhosis." (<3 mm in diameter) ***(Heidelbaugh and Bruderly, 2006).***

▪ Pathogenesis:

The diseases that lead to cirrhosis do so because they injure and kill liver cells, and the inflammation and repair that is associated with the dying liver cells causes scar tissue to form. The liver cells that do not die multiply in an attempt to replace the cells that have died. This results in clusters of newly-formed liver cells (regenerative nodules) within the scar tissue ***(Sørensen et al., 2003).***

Recent research shows the pivotal role of the stellate cell, (cell type that normally stores vitamin A) in the development of cirrhosis. Damage to the hepatic parenchyma leads to activation of the stellate cell, which becomes contractile (called myofibroblast) and obstructs blood flow in the circulation. In addition, it secretes transforming growth factor-β1 (TGF-β1), which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it secretes naturally occurring tissue inhibitors of matrix metallo-proteinases (TIMP 1 and 2,) which prevents them from breaking down fibrotic material in the extracellular matrix ***(Heidelbaugh and Bruderly, 2006).***

The liver cells that produce matrix are Hepatic Stellate Cells (HSC). This resident cell population exists in a resting phenotype as the body's major store of vitamin A. However on activation they transform to adopt a myofibroblast phenotype capable of secreting collagen. This fibrous tissue can then be remodeled through digestion of matrix by matrix metaloproteinases (MMPs). Liver fibrosis, previously thought to be merely the accumulation of scar tissue, is now recognized to be a dynamic process that can progress or regress over periods as short as months ***(Friedman, 2008).***

A key feature of hepatic fibrosis is the activation and proliferation of hepatic stellate cells, which become contractile, produce extracellular matrix components and secrete pro-inflammatory cytokines and chemokines such as transforming

growth factor beta (TGF-ß). Hepatic stellate cell activation depends on signalling by Kupffer cells, endothelial cells, hepatocytes, and platelets. The deposition of the extracellular matrix is constantly opposed by degradation of these proteins. In progressive liver fibrosis, this balance is skewed in favor of excess extracellular matrix deposition ***(Friedman et al., 2007).***

▪ Epidemiology:

Liver cirrhosis is a leading cause of death worldwide. It is the end result of a long-lasting process, usually clinically silent and unnoticed by the patient and the physician for years. Therefore, incidence and prevalence are not exactly known. In the past, up to 30–40% of cases have been discovered at autopsy. Due to the widespread use of imaging techniques, such as ultrasound and computed tomography it may be assumed that currently most cirrhotic livers are discovered earlier ***(Dancygier, 2010).***

Moreover, geographical differences in causes, variations in incidence and prevalence from one country to another, and even between different regions in the same country, make an accurate epidemiological estimate very difficult ***(Dancygier, 2010).***

Cirrhosis and chronic liver disease were the 10th leading cause of death for men and the 12th for women in the United States in 2001, killing about 27,000 people each year

(Anderson and Smith, 2010). Also, the cost of cirrhosis in terms of human suffering, hospital costs, and lost productivity is high. Established cirrhosis has a 10-year mortality of 34 - 66%, largely dependent on the cause of cirrhosis; alcoholic cirrhosis has a worse prognosis than primary biliary cirrhosis and cirrhosis due to hepatitis. The risk of death due to all causes is increased twelvefold; if one excludes the direct consequences of the liver disease, there is still a fivefold increased risk of death in all disease categories ***(Sørensen et al., 2003).***

Little is known on modulators of cirrhosis risk, apart from other diseases that cause liver injury (such as the combination of alcoholic liver disease and chronic viral hepatitis, which may act synergistically in leading to cirrhosis). Studies have recently suggested that coffee consumption may protect against cirrhosis, especially alcoholic cirrhosis ***(Klatsky et al., 2006).***

- **Etiology:**

There are many causes of cirrhosis which are summarized in (table 1).

Table (1): Showing the various causes of liver cirrhosis ***(Dancygier, 2010):***

- **Infectious**
  - Virus hepatitis B, C, D
- **Autoimmune**
  - Autoimmune hepatitis
  - Primary biliary cirrhosis
  - Autoimmune cholangitis
  - Overlap syndromes
- **Metabolic-toxic**
  - Ethanol
  - Nonalcoholic fatty liver disease (insulin resistance; metabolic syndrome)
  - Indian childhood cirrhosis
- **Drug-induced**
  - e.g.arsenic, methotrexate, isoniazid, amiodarone.
- **Genetic–hereditary**
  - Hereditary hemochromatosis
  - Wilson's disease
  - a1-antitrypsin-deficiency
  - Porphyria cutanea tarda
  - Glycogen storage diseases
  - Galactosemia
  - Tyrosinemia
  - Urea cycle disturbances
  - Abetalipoproteinemia
  - Cystic fibrosis
- **Biliary**
  - Secondary biliary cirrhosis (gallstones, strictures)
  - Primary sclerosing cholangitis
  - IgG4-associated cholangitis
  - Ischemic cholangiopathy
  - Ductopenia, bile duct atresia
  - Alagille's syndrome
- **Vascular**
  - Chronic right heart failure
  - Constrictive pericarditis
  - Budd-Chiari syndrome
  - Sinusoidal obstruction syndrome (venoocclusive disease)
  - Hereditary hemorrhagic telangiectasia (Osler-Rendu-Weber disease)
- **Cryptogenic**

▪ Clinical Manifestations:

The clinical spectrum of liver cirrhosis ranges from asymptomatic patients with normal laboratory findings, in whom the diagnosis of cirrhosis is made incidentally, to patients with decompensated disease and hepatic failure. At the time of diagnosis, the majority of patients have compensated cirrhosis, and physical examination discloses signs of chronic liver disease. A minority of patients initially present with decompensated disease manifested for example by ascites, esophageal variceal bleeding, signs of hepatic encephalopathy or the systemic manifestations of hepatocellular carcinoma ***(Heidelbaugh and Bruderly, 2006).***

Some of the signs and symptoms may occur in the presence of cirrhosis or as a result of the complications of cirrhosis. Many are nonspecific and may occur in other diseases and do not necessarily point to cirrhosis. Likewise, the absence of any does not rule out the possibility of cirrhosis: ***(Dancygier, 2010).***

- Weakness, fatigue, anorexia, weight loss.
- Jaundice: is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae and other mucous membranes caused by hyperbilirubinemia

(increased levels of bilirubin in the blood concentration higher than 1.8 mg/dL.

- Spider nevi**:**Vascular lesions consisting of a central arteriole surrounded by many smaller vessels because of an increase in estradiol. These occur in about 1/3 of cases.
- Palmar erythema: Exaggerations of normal speckled mottling of the palm, because of altered sex hormone metabolism.
- Itching: because of bile salt products deposited in the skin
- Nail changes, These include:

  1- Muehrcke's lines**:** paired horizontal bands separated by normal color resulting from hypoalbuminemia (inadequate production of albumin.

  2- Terry's nails: proximal two thirds of the nail plate appears white with distal one-third red, also due to hypoalbuminemia.

  3- Clubbing**:** angle between the nail plate and proximal nail fold > 180 degrees. It is associated with a number of diseases, mostly of the heart and lungs. Idiopathic clubbing can also occur, and in 60% of cases there is no associated underlying disease.

- Bruising and bleeding: resulting from decreased production of Vitamin K dependent coagulation factors**,** II, VII,IX, X.
- Hypertrophic osteoarthropathy: Chronic proliferative periostitis of the long bones that can cause considerable pain.
- Dupuytren's contracture: Thickening and shortening of palmar fascia that leads to flexion deformities of the fingers. Thought to be caused by fibroblastic proliferation and disorderly collagen deposition. It is relatively common in 33% of patients.
- Gynecomastia: Benign proliferation of glandular tissue of male breasts presenting with a rubbery or firm mass extending concentrically from the nipples. This is caused by increased estradiol and can occur in up to 66% of patients.
- Hypogonadism: Manifested as impotence, infertility, loss of sexual drive, and testicular atrophy because of primary gonadal injury or suppression of hypothalamic or pituitary function.
- Liver size. Can be enlarged, normal, or shrunken.
- Splenomegaly: Caused by congestion of the red pulp as a result of portal hypertension.

- Ascites**:** Accumulation of fluid in the peritoneal cavity giving rise to flank dullness (needs about 1500 mL to detect flank dullness).
- Caput medusa**:** In portal hypertension, periumbilical collateral veins may dilate. Blood from the portal venous system may be shunted through the periumbilical veins and ultimately to the abdominal wall veins, manifesting as caput medusa.
- Cruveilhier-Baumgarten murmur**:** Venous hum heard in epigastric region (on examination by stethoscope) because of collateral connections between portal system and the periumbilical veins in portal hypertension.
- Fetor hepaticus**:** Musty odor in breath as a result of increased dimethyl sulfide.

Table (2): Showing manifestations of liver cirrhosis ***(Friedman, 2008).***

Finding	Comment
Ascites	Portal hypertension
Hepatomegaly	Facultative; small liver in posthepatitic cirrhosis
Splenomegaly	Portal hypertension
Skin Changes	
○ **Glazing lips and tongue**	Skin atrophy; papillary atrophy
○ **Oral rhagades**	Zinc deficiency
○ **Spider angiomas**	Central arteriole with radiating vessels
○ **"Banknote" skin**	Skin atrophy due to zinc deficiency
Palmar erythema	↑estrogen: testosterone (?)
Dupuytren's disease	Palmar fibromatosis; occurs predominantly in alcoholics
Jaundice	Advanced hepatocellular failure.
Purpura	Vascular fragility Thrombocytopenia.
Scratch signs	Pruritus
Xanthelasms	Chronic biliary/cholestatic diseases
↑Abdominal venous cutaneous vessels	Portal hypertension
Caput medusae	Portal hypertension
Nail Changes	
○ **White nails**	Predominantly thumb and index finger
○ **Clubbed fingers/hour glass nails**	In hepatopulmonary syndrome
Endocrine Changes	
○ **Abdominal baldness**	Feminization in men
○ **↓Terminal hair in men**	Increased ratio of estrogen to free androgen due to decreased testosterone production, and increased peripheral conversion of testosterone to estradiol.
○ **Testicular atrophy**	
○ **Gynecomastia**	
○ **Amenorrhea**	
○ **Miscellaneous**	
Foetor hepaticus	Intestinal methylmercaptanes (?)
Kayser Fleischer Ring	Green-brown corneal ring; Wilson's disease Cytokines (?).
Muscle atrophy	Malnutrition
Parotid gland swelling	Malnutrition; predominantly in Alcoholics

- **Laboratory findings:** ***(Foucher et al., 2006).***

1- Aminotransferases: AST and ALT are moderately elevated, with AST > ALT. However, normal aminotransferases do not preclude cirrhosis.

2- Alkaline phosphatase: usually slightly elevated.

3- Gamma-glutamyl transferase: correlates with AP levels. Typically much higher in chronic liver disease from alcohol.

4- Bilirubin: may elevate as cirrhosis progresses.

5- Albumin: levels fall as the synthetic function of the liver declines with worsening cirrhosis since albumin is exclusively synthesized in the liver

6- Prothrombin time: increases since the liver synthesizes clotting factors, II, VII, IX, X.

7- Globulins: increased due to shunting of bacterial antigens away from the liver to lymphoid tissue.

8- Serum sodium: hyponatremia due to inability to excrete free water resulting from high levels of ADH and aldosterone.

9- Thrombocytopenia: due to both congestive splenomegaly as well as decreased thrombopoietin from the liver. However, this rarely results in platelet count < 50,000/mL.

10- Leukopenia and neutropenia: due to splenomegaly with splenic margination.