Study of diagnostic value of plasma Malondialdehyde And severity of Portal Hypertension In Egyptian cirrhotic patients

Thesis

Submitted for Partial Fulfillment of Master Degree in Internal Medicine

By

Sherif Ahmed Megahed Ahmed

MB.B.Ch. Ain Shams University, 2012

Under Supervision of

Prof. Dr. Samir Abd Elhamid Ghait

Professor of Internal Medicine, Hepatology and Gastroenterology
Faculty of Medicine, Ain Shams University

Dr. Inas El khedr Mohammed

Assistant Prof. of Internal Medicine, Hepatology and Gastroenterology
Faculty of Medicine, Ain Shams University

Dr. Ayman Gamil Anwar

Lecturer of Internal Medicine, Hepatology and Gastroenterology
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2016

INTRODUCTION

Portal hypertension is one of the major occurrence and death reasons of patients with liver cirrhosis. The major pathophysiology of portal hypertension is the rising of the portal vein blood flow resistance which is partly caused by the liver structure alteration and the blood structure alteration as well **(Parola and Robino, 2007)**.

In the progress of cell necrosis, inflammation and death, oxidative stress response is integrated with the protein, damaging DNA and reacting with the cell chemical composition to cause the cell damage **(Boonstra and Post, 2004).**

Oxidative stress (OS) refers to a condition under which organism or cell reactive oxygen species (ROS) are excessively produced and the antioxidant defense function is weakened, which causes big imbalance and damage the organism cell **(Catapano et al., 2000).**

It had been proved that oxidative stress response speed up the development of liver fibrosis and lead to the initiation of the hepatic epithelioid malfunction, which is adjusted by the bioavailability of NO in the intrahepatic microcirculation **(Rodriguez-Vilarrupla et al., 2007).**

Malondialdehyde (MDA), a typical aldehydic product of lipid peroxidation, results from lipid peroxidation of polyunsaturated fatty acids. The degree of lipid peroxidation can be estimated by the amount of MDA in tissues and it is a marker for oxidative stress **(Jain et al., 2002).**

The current gold standard for measuring PHT and its severity is measurement of the hepatic venous pressure gradient (HVPG)**.** HVPG is also emerging as a reliable endpoint to assess disease progression and therapeutic response in chronic liver disease (**Groszmann et al., 2005)**

Aim of the work

To study the value of plasma Malondialdehyde (MDA), a lipid peroxide marker for oxidative stress, as a diagnostic biomarker for severity of Portal Hypertension in Egyptian cirrhotic patients.

Liver Cirrhosis

Definition of Liver Cirrhosis:

Liver cirrhosis is a late stage of progressive hepatic fibrosis is characterized by distortion of the architecture and formation of regenerative nodules and different degrees of liver function impairment; these patients are prone to a variety of complications reducing life expectancy markedly ***(Sørensen et al., 2003).***

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 refers to the orange or tawny surface of the liver seen at autopsy. Cirrhosis is defined histopathologically as a diffuse hepatic process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules (***David et al.,2011)***.

The World Health Organization (WHO) indicates that 10% of the world population has chronic liver disease; this represents approximately 500 million people, Two million people worldwide die each year from hepatic failure ***(Schuppan and Afdhal ,2008).***

In the developed countries alcoholic liver disease (ALD), hepatitis C virus infection (HCV) and non-alcoholic steatohepatitis (NASH) are the most significant causes of cirrhosis ***(Wynn, 2008).***

Etiology and risk factors:

The main causes of cirrhosis worldwide are:

- Alcoholic liver disease (ALD).
- Viral heparitis.
- Nonalcoholic steatohepatitis (NASH),
- Haemochromatosis,
- Wilson disease
- Autoimmune hepatitis (AIH),
- Primary biliary cirrhosis (PBC)
- Primary sclerosing cholangitis (PSC)
- Genetic casuses
- Drug induced
- Other rare causes.

(Guha and Iredale, 2007).

Viral hepatitis

Hepatitis B is a DNA virus, unlike the other common hepatotropic viruses, which are RNA viruses. It may occur as a discrete entity or as co-infection with hepatitis D, or delta infection. Although hepatitis B usually presents as a mono-infection, its presence is necessary for the delta virus to be infective, hepatitis B virus may lead to chronic liver disease and cirrhosis ***(Lok and McMahon, 2007).***

Hepatitis C is an RNA virus that may cause chronic infection in 80% of patients and cirrhosis in 15% of patients. The propensity to cirrhosis in patients with hepatitis C is increased in alcoholic patients ***(Leandro et al., 2006).***

Egypt is home to the highest prevalence of hepatitis C virus (HCV) in the world with an overall rate of 22%, In the population aged older than 40-60 years, the majority of infection can be explained by the intravenous treatment for schistosomiasis and other iatrogenic exposures as blood transfusion ***(El-Zayadi, 2004).***

Alcohol

Alcohol is one of the leading causes of liver cirrhosis in the Western World. The risk of acquiring alcohol cirrhosis has been suggested to increase when alcohol intake increases, it has been estimated that the risk of liver injuries increases when the consumption exceeds 40 g/day**,** which is equal to 1.1 L of bear, 0.44 L of wine or 0.11 L of spirits ***(Savolainen et al., 1993 and Gunnarsdóttir, 2008).***

Nonalcoholic fatty liver disease (NAFLD)

The spectrum of NAFLD includes nonalcoholic steatohepatitis, which can lead to fibrosis and cirrhosis. The only valued treatment available at present is weight reduction along with correction of lipid and glucose abnormalities. The growing numbers of patients with obesity seems to guarantee that more patients will progress to cirrhosis at an earlier age in the future ***(Wanless and Shiota, 2004).***

Autoimmune causes

Autoimmune hepatitis is a chronic hepatitis that occurs in children and adults of all ages. Its pathogenesis include environmental triggers, a failure of immune tolerance mechanisms, and a genetic predisposition collaborating to induce a T cell-mediated immune attack upon liver antigens, leading to a progressive necro-inflammatory and fibrotic process in the liver with the presence of circulating autoantibodies and high serum globulin concentrations ***(Michael et al., 2010).***

Autoimmune hepatitis, an inflammatory condition of the liver, has unknown etiology and causes progressive liver dysfunction. The presence of anti-smooth muscle antibodies, antinuclear antibodies, and increased serum gamma globulins help suggest the diagnosis. Other autoimmune disorders may also be present (Sjögren syndrome, thyroiditis, glomerulonephritis). Patients not responding to steroids and immune suppressive therapy may progress to cirrhosis ***(Czaja, 2008).***

Biliary cirrhosis:

Primary biliary cirrhosis (PBC), a disorder that often affects middle-aged women which is characterized by cholestatic liver enzymes and positive antimitochondrial antibodies. Treatment for primary biliary cirrhosis depends on how early diagnoses and presence of complications. In the early, treatment can slow the progression of liver damage to cirrhosis and prevent complications ***(Kumagi et al., 2008).***

Primary sclerosing cholangitis:

Primary sclerosing cholangitis (PSC) typically affects young men. It may occur up to 80% of the time with inflammatory bowel disease (especially ulcerative colitis) or as a primary entity. There is no specific serologic marker, and diagnosis is usually made by noting a pruned tree deformity of bile ducts on ERCP or MRCP ***(Lindor, 2007).***

Wilson disease:

Wilson disease (hepatolenticular degeneration) is an autosomal recessive defect in cellular copper transport. An impairment in biliary excretion leads to the accumulation of copper in the liver. Over time the liver is progressively damaged and becomes cirrhotic ***(Roberts and Schilsky, 2008),*** Once cirrhosis occurs, copper leaks into plasma, accumulates in and damages other tissues, and causes multitude of signs and symptoms of neurologic, hematologic and renal disease ***(Roberts and Schilsky, 2008).***

Genetic disorders

The genetic diseases α1-antitrypsin deficiency, Wilson disease, and hemochromatosis may be associated with cirrhosis. Because these diseases have a hereditary basis, all family members should be screened when a diagnosis is made in one family member. These diseases accounted for -cryptogenic cirrhosis in the past. Cirrhotic with emphysema and children with cholestasis should be evaluated for α 1-antitrypsin deficiency ***(Perlmutter, 2004).***

Some less common reported causes of cirrhosis are

- Drugs as α -Methyldopa, Methotrexate & Nitrofurantoin.
- Hypervitaminosis A.
- Type IV Glycogen storage diseases as hereditary tyrosinemia & Mucopolysaccharoidosis.
- Infections as Syphilis and Schistosomiasis.
- Granulomatous disease (e.g. sarcoidosis).
- Graft-versus-host disease.
- Venous outflow obstruction (e.g. Budd-Chiari syndrom)
- Chronic congestive right-sided heart failure.
- Tricuspid regurgitation.
- Secondary biliary cirrhosis (associated with chronic extrahepatic bile duct obstruction).
- Poisons (ex : herbicide paraquat)

(David, 2011).

Ten to 15% of cases of cirrhosis remain -cryptogenic when no etiology can be easily identified; however, it is almost considered a vanishing entity ***(Angulo, 2002).***

Pathophysiology:

The liver plays a vital role in synthesis of proteins (e.g., albumin, clotting factors and complement), detoxification and storage (e.g., vitamin A). In addition, it participates in the metabolism of lipids and carbohydrates. Cirrhosis is often preceded by hepatitis and fatty liver (steatosis), independent of the cause. If the cause is removed at this stage, the changes are still fully reversible. The pathological hallmark of cirrhosis is the development of scar tissue that replaces normal parenchyma, blocking the portal flow of blood through the organ and disturbing normal function. Recent research shows the pivotal role of the stellate cell, a 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 TGF-β1, which leads to a fibrotic response and proliferation of connective tissue. Furthermore, it secretes TIMP 1 and 2, naturally occurring inhibitors of matrix metalloproteinases, which prevents them from breaking down fibrotic material in the extracellular matrix ***(Iredale, 2003).***

Pathology

Macroscopically, the liver is initially enlarged, but with progression of the disease, it becomes shrunken. Its surface is irregular, the consistency is firm and the color is often yellow (if associates steatosis) as seen in **Fig. (1)**. Depending on the size of the nodules there are three macroscopic types: micronodular, macronodular and mixed cirrhosis ***(Brenner et al., 2003).***

In micronodular form (Laennec's cirrhosis or portal cirrhosis) regenerating nodules are under 3 mm. In macronodular cirrhosis (post-necrotic cirrhosis), the nodules are larger than 3 mm. The mixed cirrhosis consists in a variety of nodules with different sizes ***(Brenner et al., 2003).***

Cirrhosis is defined by its pathological features on microscopy:

(1) The presence of regenerating nodules of hepatocytes.
(2) The presence of fibrosis, or the deposition of connective tissue between these nodules.

The pattern of fibrosis seen can depend upon the underlying insult that led to cirrhosis, fibrosis can also proliferate even if the underlying process that caused it has resolved or ceased. The fibrosis in cirrhosis can lead to destruction of other normal tissues in the liver: including the sinusoids, the space of Disse, and other vascular structures, which leads to altered resistance to blood flow in the liver and portal hypertension ***(Brenner et al., 2003).***

Figure (1): Gross picture of liver cirrhosis ***(Jonas et al., 2001)***

Clinical consequence of cirrhosis:

A-Liver cell failure

- **Coagulopathy:** The liver plays a central role in the clotting process. Acute and chronic liver diseases are invariably associated with coagulation disorders due to multiple causes such as decreased synthesis of clotting and inhibitor factors, decreased clearance of activated factors, quantitative and qualitative platelet defects, hyperfibrinolysis and accelerated intravascular coagulation. This leads to increased risk of morbidity and mortality in patients undergoing diagnostic or therapeutic invasive procedures ***(Kim et al., 2010).***

- **Jaundice:** The clinician may first recognize cutaneous and scleral yellowing, which indicates the inability to clear bilirubin ***(Harvey et al., 2009).***

- **Hypoalbuminemia:** cirrhosis leads to impairment of synthetic functions of the liver which leads to decrease synthesis of albumin in hepatic cells which may lead to serious complications such as ascites, lower limb edema and muscle weakness ***(Kim et al., 2010).***

- **Cutaneous manifestations*:*** Spider angiomas, collections of small vessels on the face, arms, and trunk may be apparent. With the decreased synthesis of clotting factors produced by the liver**.** Nail bed changes of paired horizontal white bands (Muehrcke nails) or nails with whitening of the proximal two thirds and reddening of the distal third (Terry nails) may be present. Digital clubbing. Thickening of the palmar fascia (Dupuytren contracture) of the hands especially in alcoholics and Itching (pruritus) because of bile salt products deposited in the skin ***(Harvey et al., 2009).***

- **Hormonal disorders*:*** Elevated estrogen levels can result in gynecomastia, and testicular atrophy. Also it causes decreased libido and infertility ***(David, 2011).***

- **Fetor hepaticus:** When there is decreased clearing by the liver of mercaptans from the circulation, a sweet odor is noticeable in the breath of patients ***(Kim et al., 2010).***

- **Ascites:** accumulation of fluid in peritoneal cavity, the two older theories of ascites formation, the underfill theory and the overflow theory, appear to be relevant at different stages of the natural history of cirrhosis. However, the most recent theory, the arterial vasodilation hypothesis, appears to match best with the actual hemodynamic data and has become the most widely accepted theory with hypoalbuminemia and portal hypertension. Ascites may become infected with bacteria normally present in the intestines (spontaneous bacterial peritonitis) ***(Kim et al., 2010).***

- **Hepatocellular carcinoma:** is a primary liver cancer and a frequent complication of cirrhosis. It has a high mortality rate. HCC is the third most common cause of cancer-related death worldwide ***(Yang, 2010).***

B- Portal hypertension

See portal hypertension chapter below.

Major complications of liver cirrhosis:

- **Hepatorenal syndrome:** insufficient blood supply to the kidneys, causing acute renal failure. This complication has a very high mortality (over 50%). As the kidneys stop functioning, toxins begin to build up in the body. Eventually, this leads to liver failure. It is *only* seen in people with severe liver damage and is almost always caused by cirrhosis ***(Charles et al., 2007)***.