INTRODUCTION

Portal hypertension is an abnormal elevation in the blood pressure within the portal circulation which is composed of the portal vein that receives blood from the entire intestine and from the spleen, pancreas, and gallbladder and carries that blood to the liver. After entering the liver, the portal vein divides into right and left branches and then into tiny channels that run through the liver. When blood leaves the liver, it flows back into the general circulation through the hepatic vein ***(Gallego et al., 2002).***

Portal hypertension is defined as the pathological elevation in portal venous pressure, in which the pressure in the portal venous system is at least 5 mm Hg higher than the pressure in the inferior vena cava. In the 17th century, it was well recognized that structural abnormalities in the hepatic portal venous system could give rise to gastrointestinal bleeding. In 1902, Gilbert and Carnot were the first to describe this condition with the expression "portal hypertension" ***(Sandblom, 1993)***.

Portal hypertension becomes clinically significant when the portal venous pressure gradient exceeds a threshold value of 10 mmHg ***(Groszmann and Wongcharatrawee, 2004).***

This elevated pressure is caused by a functional resistance to blood flow at any part of portal venous system

starting from portal vein ant its tributaries through the hepatic veins and inferior vena cava up to the right atrium. It can be caused also by an increase in blood flow in the portal venous system ***(Garcia-Pagan et al., 2012).***

This process may result into many vascular decompensation complications which may be serious such as variceal bleeding and clinical decompensation such as hepatic encephalopathy and ascites ***(Ripoll et al., 2007)***. Gastroesophageal variceal bleeding is a direct consequence of portal hypertension that leads to significant mortality and morbidity among patients with cirrhosis ***(Said et al., 2012)***.

Liver biopsy has traditionally been considered the reference method for evaluation of tissue damage such as hepatic fibrosis in patients with chronic liver disease. Pathologists have proposed robust scoring system for staging liver fibrosis such as the semi-quantitative METAVIR score ***(Bedossa and Poynard, 1996).***

Liver biopsy is an invasive procedure carrying a risk of rare but potentially life-threatening complications. These limitations have led to the development of non-invasive methods for assessment of liver fibrosis. Although some of these methods are now commonly used in patients for first line assessment ***(Bravo et al., 2001).***

Oxidative stress has been related to the etiopathogenesis of several chronic diseases and plays a paramount role in the aging process ***(Ceconi et al., 2003; Sohal et al., 2002).*** Of the many biological targets of oxidative stress, lipids are the most involved class of biomolecules. Lipid oxidation gives rise to a number of secondary products. These products are mainly aldehydes, with the ability to exacerbate oxidative damage ***(Kunsch and Medford, 1999)***. Longevity and high reactivity allow these molecules to act inside and outside the cells, interacting with biomolecules such as nucleic acids and proteins, often irreversibly damaging the delicate mechanisms involved in cell functionality.

Malondialdehyde (MDA), a typical aldehydic product of lipid peroxidation, results from lipid peroxidation of polyunsaturated fatty acids ***(Davey et al., 2005).*** The degree of lipid peroxidation can be estimated by the amount of MDA in tissues and it is a marker for oxidative stress. MDA had been proved to be up-expression significantly in cirrhotic patients ***(Uchida, 2000).*** Liver diseases have been reported to be related to oxidative stress. Plasma MDA concentrations were higher in cirrhotic patients with viral hepatitis than in matched healthy controls ***(Loguercio and Federico, 2003).*** At present, the relationship between oxidative stress and portal hypertension in the liver cirrhotic patients is still undefined.

AIM OF THE WORK

The aim of this study is to evaluate the relevance between the malondialdehyde (MDA) level and portal hypertension in cirrhotic patients and to reveal the potential role of MDA as an important non-invasive diagnostic method in cirrhotic patients with portal hypertension.

PORTAL HYPERTENSION

When studying the history of portal hypertension (PH) by the inquisitive spirit and the intuition of early investigators who, with simple technical means, acquired a surprising degree of knowledge and understanding. Thus, as early as 1543, Vesalius drew an anatomical picture of the portal venous system. In the 1650s, Harvey's discovery of the blood circulation, Glisson at a dissection in London, established the portal vein as the vessel by which blood was collected from the gastrointestinal tract and returned to the systemic circulation ***(Glisson, 1955)***.

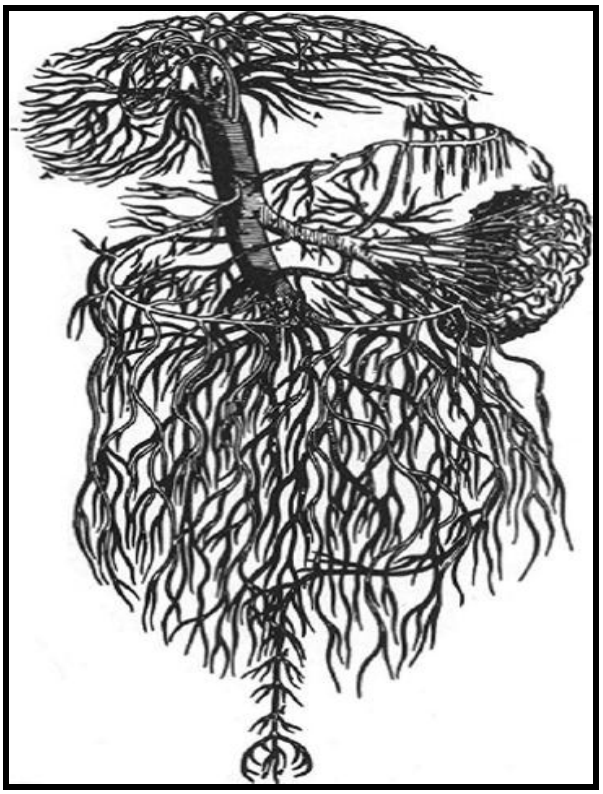

Figure (1): Vesalius's pictorial of the portal venous system ***(Vesalius, 1543).***

What is portal hypertension?

Portal hypertension is a term used to describe elevated pressure in the portal venous system. Normal portal vein pressure ranges from 5–10 mm Hg, Pressure within the portal system is dependent upon both input from blood flow in the portal vein, and hepatic resistance to outflow ***(Bloom et al., 2015).***

Anatomy of Portal Circulation

Portal circulation is the unique circulatory system, which connects two systems of capillary beds; one in the wall of the small intestine and spleen and the second in sinusoidal area of the liver. The portal venous system is responsible for directing blood from parts of the gastrointestinal tract to the liver ***(Baveno, 2005)***.

The portal venous system includes all veins which carry blood from subphrenic part of digestive tract: from pancreas, gallbladder and spleen to the liver. The portal vein is formed by the splenic vein, superior mesenteric vein and divides into a right and a left branch immediately before entering the liver and then into tiny channels that run through the liver. The left gastric vein is the significant branch of the portal vein which plays an important role in pathophysiology of portal hypertension and in formation of esophageal varices ***(Cardenas and Ginem, 2005)***.

The inferior mesenteric vein, which drains the distal third of the transverse colon, descending colon, sigmoid colon, rectum, and upper part of the anal canal, enters the splenic vein SV before the junction of the SV and SMV. The SV originates at the splenic hilum. The short gastric and posterior gastric veins drain the fundus of the stomach and enter the SV near the tail of the pancreas. The left gastroepiploic vein and pancreatic veins also enter the SV. The left and right gastric veins, which run along the lesser curvature of the stomach, usually drain into the portal vein immediately after the junction of the SV and SMV. The paraumbilical veins and remnants of the umbilical vein drain into the left portal vein ***(Floch and Netter, 2010)***.

Blood passes from branches of the portal vein through sinusoids of the liver. Blood also flows from branches of the hepatic artery and mixes in the sinusoids to supply the hepatocytes with the following figure.

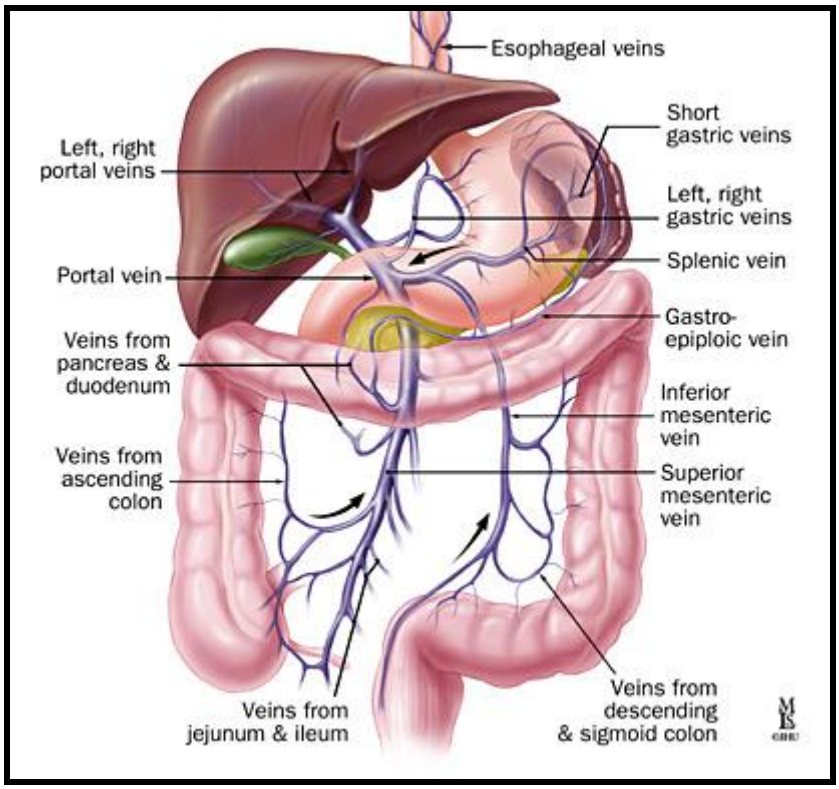

Figure (2): Anatomy of portal venous system ***(Podolsky et al., 2015).***

The PV has a segmental intrahepatic distribution, accompanying the hepatic artery. At the hilum, main PV (MPV) divides into larger right and left PV branches (RPV and LPV). The RPV then divides into anterior (RAPV) and posterior (RPPV) trunks. RAPV supplies Segments V and VIII. RPPV supplies Segments VI and VII. The left PV (LPV) initially has a horizontal course to the left and then it turns medially towards the ligamentum teres giving branches to supply Segments II, III and IV and the caudate lobe. Normal portal blood flow in human beings is about 1000–1200 ml min. The portal vein supplies about 75% of the blood

flow to the liver, while the hepatic artery provides the remainder of hepatic blood flow. Normal portal pressure is about 7 mmHg ***(Binit et al., 2015)***.

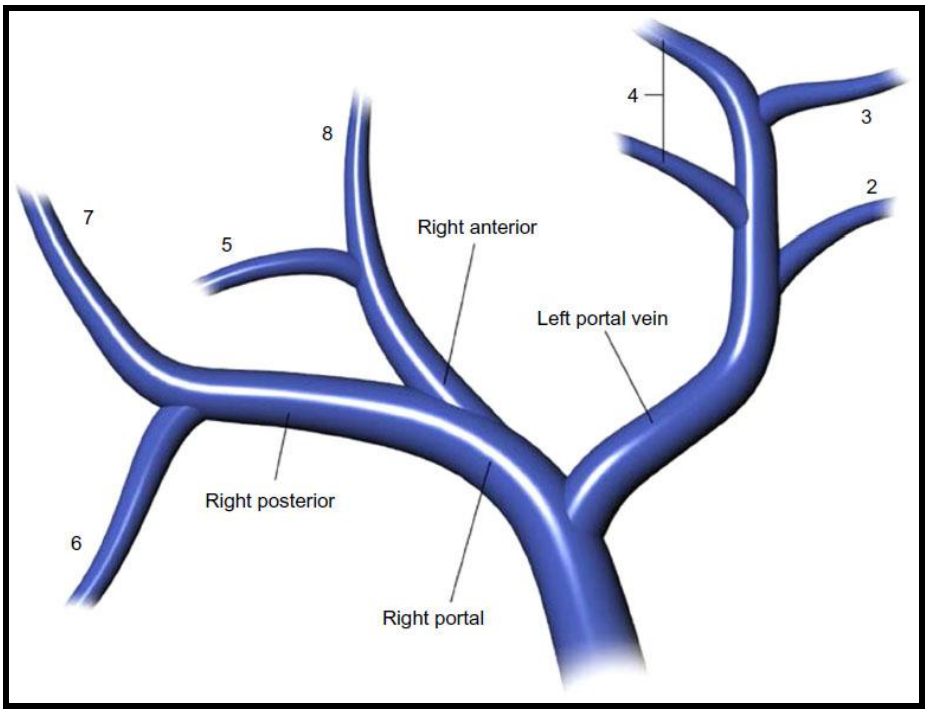

Figure (3): Portal venous anatomy to the liver ***(Luersen et al., 2015).***

The hepatic veins drain blood from the liver. Hepatic veins are divided into an upper and a lower group. The upper three drain the central veins from the right, middle, and left regions of the liver and are larger than the lower group of veins. The lower group of hepatic veins form from six to twenty smaller hepatic veins come from the right lobe and the caudate lobe, are in contact with the hepatic tissue, and are valveless. All the veins empty into the inferior vena cava at the back of the liver ***(Fang et al., 2012)***.

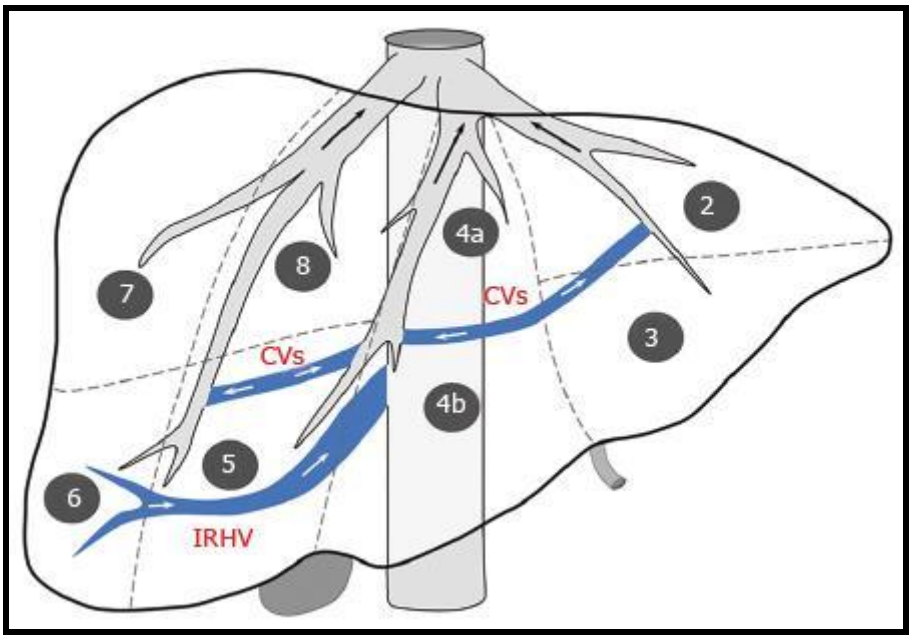

Figure (4): Diagram of liver segmentation and the anatomical variations of hepatic venous outflow ***(Alvarez et al., 2016).***

Portosystemic anastomosis:

When the portal venous pressure gradient exceeds a certain threshold, collaterals develop at sites of communication between the portal and systemic circulations, and blood will flow in a reverse direction to reach systemic circulation. The five areas of portosystemic anastmosis are as follows ***(Sherlock and Dooley, 2011)***:

1- At the lower end of the esophagus, where the left gastric vein of the portal system anastomoses with the azygous system of veins which drains the middle third of the esophagus into systemic circulation.

2- In the paraumbilical region, where the paraumbilical veins in the falciform ligament anastomose with the superficial veins of the anterior abdominal wall.

3- In the splenic venous bed and the left renal vein.

4- In the retroperitoneum.

5- At the anal canal, where the superior hemorrhoidal vein of the portal system anastomoses with the middle and inferior hemorrhoidal veins of the caval system ***(Moubarak et al., 2011)***.

Gastroesophageal collaterals are of important clinical significance due to the risk of rupture and variceal hemorrhage ***(Sherlock and Dooley, 2011).***

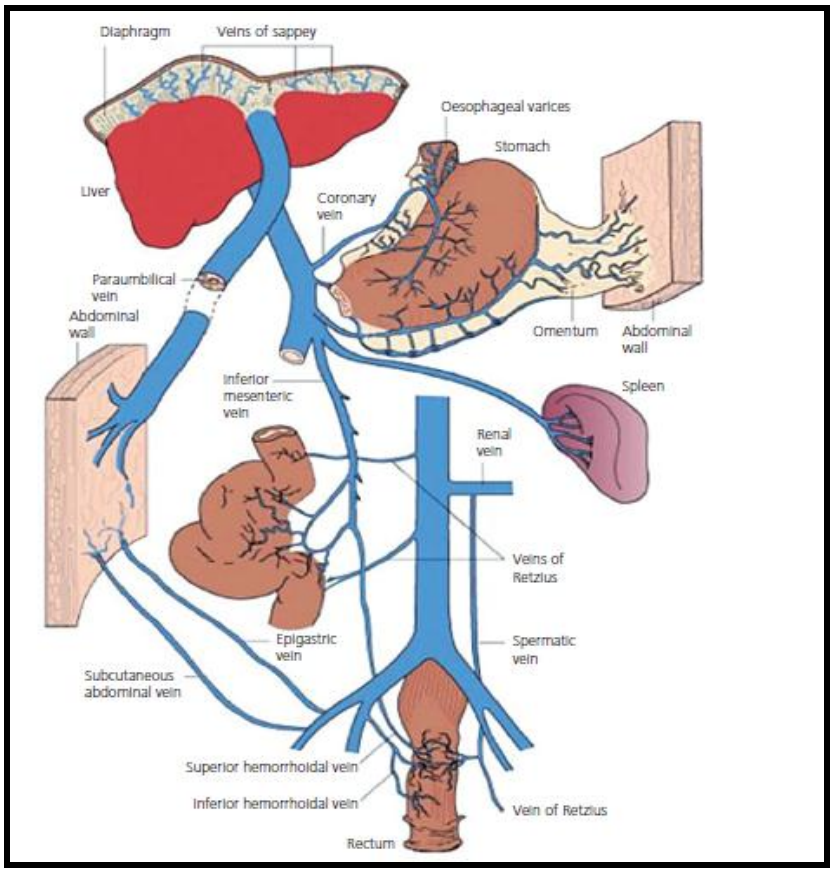

Figure (5): Sites of portosystemic collateral circulation in portal hypertension and cirrhosis ***(Sherlock and Dooley, 2011)***.

Pathophysiology of Portal Hypertension

Many researches have influenced the opinions on the pathophysiology of portal hypertension. They suggest several causative mechanisms contributing to hypertension developing in the portal circulation. It was observed that formation of collateral circulation that decompresses portal venous system does not decrease portal pressure. Those facts undoubtedly suggest that other mechanisms besides anatomical occlusion are

involved in developing portal hypertension ***(Gonciarz and Mazur, 2006)***.

From the point of view of physics blood pressure determined in the vascular bed is defined by a simple formula: pressure = vascular resistance x blood flow

Thus etiopathogenetic pressure is a resultant from increased vascular resistance and/or increased volume of blood flowing through the portal vascular bed. Vascular resistance increases due to difficult outflow of the blood from the portal bed to the hepatic veins and inferior vena cava mainly as a consequence of mechanical occlusion. Its location and size depend on the cause and hemodynamic efficiency of the portal-systemic circulation ***(Gonciarz and Mazur, 2006)***.

Another significant factor decisive of portal pressure is increased blood flow in the portal circulation. It is connected with so called hyperkinetic circulation, which is manifested as increase cardiac output volume and generalized vasodilation of the vascular bed (increased volume of systemic circulation) ***(Tsai, 2007)***.

The mechanism of enlarged visceral bed has not been clearly described. Portal hypertension is associated with changes in the intrahepatic, systemic, and portosystemic collateral circulation. Alterations in vasoreactivity (vasodilation and vasoconstriction) play a central role in the pathogenesis of

portal hypertension by contributing to increased intrahepatic resistance, hyperdynamic circulation, and expansion of the collateral circulation, Portal hypertension is also importantly characterized by changes in vascular structure; termed vascular remodeling, which is an adaptive response of the vessel wall that occurs in response to chronic changes in the environment. These complementary processes of vasoreactivity and vascular remodeling contribute importantly to increased intrahepatic resistance and represent important targets in the treatment of portal hypertension ***(Shah, 2007)***.

Biologically active vasodilators that increase portal flow seem to play an important role. They include nitric oxide (NO), glucagons, prostaglandins, bile acids, Tumor necrosis factor α, and carbon monoxide. It is their dysfunction that differentiates the response of the vascular bed in the form of vasodilation or vasoconstriction ***(Zipprich, 2007)***.

Thus, the imbalance between the hyperresponsiveness and overproduction of vasoconstrictors (mainly endothelin-1and cyclooxygenase-derived prostaglandins) and the hyporesponsiveness and impaired production of vasodilators (mainly NO) are the mechanisms responsible of the increased vascular tone in the sinusoidal/postsinusoidal area ***(Brzozowski et al., 2005)***.

Some investigations have found different availabilities of NO in the intrahepatic circulation with preserved production in

the presinusoidal area and impaired production in the sinusoidal/postsinusoidal area. Decreased vascular resistance in the presinusoidal area of the liver is caused by increased concentrations of NO and adenosine. In case of portal hypertension however NO is not produced in the presinusoidal system and its production is disturbed or substantially decreased in the sinusoidal/postsinusoidal area ***(Watanabe et al., 2007)***.

Thus altered vascular vasoreactivity has to be considered an important pathogenetic factor of portal hypertension which produces vasoconstriction or vasodilation that cause increased vascular resistance, hyperkinetic circulation and formation of collateral portal circulation ***(Shah, 2007)***.

Another research has found other factors that determine the flow of blood within the portal bed responsible for increased portal pressure. Vitamin A-rich hepatic stellate cells (HSC) seem to be very important ***(Reeves and Friedman, 2002)***.

They make up 13-15% all hepatic cells and once activated they play the role of miofibroblasts and are considered to be the main source of collagen, fibronectin and other components of extracellular matrix (ECM). HSCs, also called Ito cells, are found in perisinusoidal spaces of the liver and significantly modulate blood flow through the hepatic sinuses. Their activity is regulated by endothelial factors: