Introduction

Portal hypertension is a major complication of liver cirrhosis and can be a direct cause of variceal hemorrhage and of bleeding related death. Therefore, esophagogastro-duodenoscopy (EGD) is considered to be necessary for all cirrhotic patients to evaluate the risk of variceal bleeding ***(De Franchis, 2005).***

Several biochemical parameters have been reported as predictors of the presence of varices. The presence of high grades of varices can be predicted by a low platelet count, Child-Pugh class B/C and spleen diameter. These may be considered as non-endoscopic predictors for the diagnosis and management of large grade varices ***(Agha et al., 2009).***

Oesophageal variceal bleeding is one of the most dreaded complications of cirrhosis because of its high mortality. The prevalence of varices in patients with cirrhosis is approximately 60-80%. The incidence of OV increases by nearly 5% per year, and the rate of progression from small to large varices is approximately 5 to 10 % per year. Increasing size of varices is associated with an increase in variceal-wall tension to a critical level at which varices rupture and cause life-threatening bleeding. The mortality rate from variceal bleeding is about 20% when patients are treated optimally in hospital. Incidence of first variceal hemorrhage ranges from

20 to 40% within two years. Recurrent bleeding occurs in 30 to 40% of patients within the next two to three days and in up to 60 % within one week. Thus, prevention of esophageal variceal bleeding remains at the forefront of long-term management of cirrhotic patients ***(Sarangapani et al., 2010)***.

It is noteworthy however that variceal haemorrhage is not confined to patients with large OV although they are more likely to bleed from ruptured varices than patients with small OV ***(Jensen, 2002).***

The American Association for the Study of Liver Disease and the Baveno V Consensus Conference on portal hypertension recommended that all cirrhotic patients should be screened for the presence of OV when liver cirrhosis is diagnosed ***(Sarangapani et al., 2010)***.

Some authors have suggested repeating endoscopy at 2-3 year intervals in patients without varices and at 1-2 year intervals in patients with small varices so as to evaluate the development or progression of the OV. However, this approach has two major limitations. Endoscopy is an invasive procedure and secondly the cost effectiveness of this approach is also questionable**.** As only 9-36% patients with cirrhosis are found to have varices on screening endoscopy. It may be more cost-effective to routinely screen patients at high risk for the presence of varices so as to reduce the

increasing burden and procedure cost of endoscopy units ***(Brennan et al., 2003)***.

Identification of non-invasive predictors of OV and portal gastropathy will enable us to carry out UGE in selected group of patients thus avoiding unnecessary intervention and at the same time not missing the patients at risk of bleeding ***(Sarwar et al., 2004).***

The value of Glycated albumin (GA) as a glycemic control marker has been validated in several studies. The half-life of albumin is approximately 15 days, and GA level is believed to reflect the glycemic change over a 2-week period ***(Koga & Kasyama, 2010).***

Glycated hemoglobin (HbA1c) is a retrospective analyst of carbohydrate metabolism reflecting the mean blood glucose levels during last 6 to 8 weeks, HbA1c determination is widely used to assess the metabolic status and to monitor the medical treatment of diabetic patients ***(Nordin & Dybkaer, 2007).***

Although the ratio of GA/HbA1c is usually close to 3, patients with chronic liver disease (CLD) have a shortened life span of erythrocytes due to the hypersplenism, thus resulting in lower HbA1c levels relative to the plasma glucose level. Conversely, the turnover period of serum albumin in CLD patients is increased to compensate for

reduced albumin production. Therefore, the GA levels in CLD patients are higher relative to the degree of glycemia ***(Koga & Kasayama, 2010).***

To our knowledge there are no enough studies that assessed the relation between GA to HbA1c ratio and the presence of oesophageal varices or its severity.

Aim of the Study

The aim of the present study is to assess the value of Glycated albumin to Glycated hemoglobin ratio in the prediction of oesophageal varices and assessing its risk of bleeding.

Portal Hypertension

Definition:

Portal hypertension is defined as a free portal vein pressure in excess of 10mm Hg.

Normal portal venous pressure is 5-10 mmHg, which is sufficient to maintain a portal flow through the hepatic sinusoids of approximately 1 liter/min ***(Henderson et al., 2004).***

Anatomical considerations about portal venous system:

The name portal vein is applied to the venous system that begins in the capillaries of the intestine and terminates as hepatic sinusoids ***(Thomas et al., 2003).***

The portal vein is formed by the union of the superior mesenteric vein and the splenic vein (splenic vein drain the splanchnic and splenic beds) just posterior to the head of pancreas at about the level of the second lumbar vertebra. It extends slightly to the right of the midline for distance of 5.5-8 cm in the free edge of lesser omentum to the portahepatis, and is 1-1.2 cm in diameter ***(Sherlock and Dooley, 2002).***

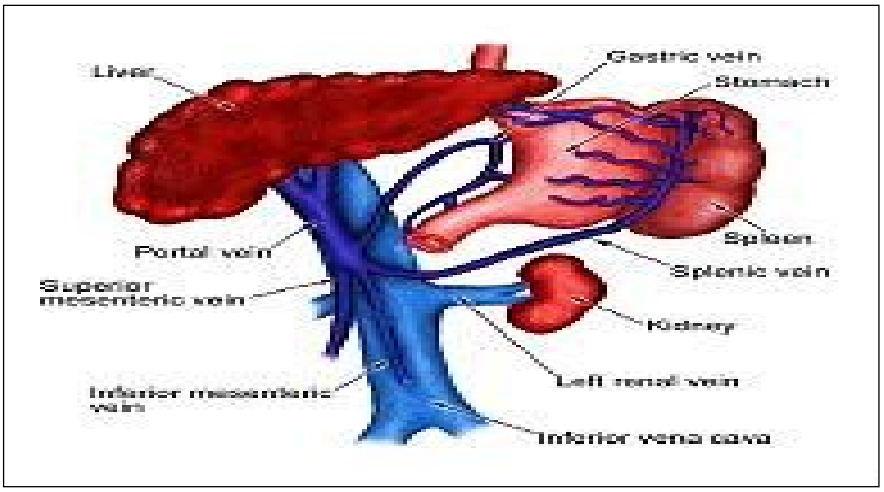

Figure (1): Anatomy of Portal circulation ***(Sherlock and Dooley, 2002).***

Physiological considerations about Portal Venous System:

The portal system is a unique system that exists between two capillary beds:

1- Upstream: The sinusoid of the spleen and capillaries of digestive tract.

2- Downstream: Sinusoidal bed of liver.

The portal blood carries the nutritive materials absorbed from the alimentary tract to the liver, it is also loaded with enzymes and hormones released in the splanchnic area, these substances are further metabolized with detoxification of toxic products before being released to the systemic circulation ***(Zakim and Boyer, 2003).***

Epidemiology:

Liver cirrhosis accounts for approximately 90 %of all cases of portal hypertension presenting in the West.

In Eastern and tropical countries non-cirrhotic causes predominate.

Distinct geographical distributions are found for non-cirrhotic portal fibrosis, schistosomiasis, and idiopathic portal hypertension ***(Bosch et al., 2003).***

Schistosomiasis affects more than 200 million people worldwide: Schistosoma mansoni is particularly prevalent in the Middle East, Africa, and South America, while S. japonicum is the causative agent in the Far East. Hepatic schistosomiasis is particularly common in Egypt, where oesophageal variceal bleeding secondary to this disease is the most common cause of upper gastrointestinal haemorrhage ***(Pybus et al., 2003).***

In children, extrahepatic portal vein obstruction is the main cause of upper gastrointestinal bleeding: this account for 40 to 50 per cent of all cases of portal hypertension in those under 17 years old. It is much more common in developing countries ***(El zayadi et al., 2001).***

Stages in the development of portal hypertension:

- Increased resistance to portal venous flow.
- Formation of portal systemic collaterals.
- Dilatation of the splanchnic venous bed and increased splanchnic flow.
- Expansion of the intravascular plasma volume
- Peripheral and splanchnic vasodilatation leading to development of a hyperkinetic systemic circulation ***(De Franchis and Primignani, 2001).***

Etiology and Classifications of Portal Hypertension:

Cirrhosis, mainly from alcohol and chronic viral hepatitis, is the most important cause of portal hypertension, but there are many other causes ***(Nathan et al., 2002).***

The causes of portal hypertension are conventionally classified according to the localization of the site of maximal resistance to portal flow.

The three major categories of portal hypertension are prehepatic, intrahepatic and post hepatic.

In case of intrahepatic causes, the site of resistance is conventionally subdivided further into presinusoidal, sinusoidal, and postsinusoidal ***(Nathan et al., 2002)***

Table (1): Etiology and Functional Classification of Portal hypertension (PHT):

1-Primary increased flow
- Arterial-portal venous fistula
- Intrahepatic
- Intrasplenic
- Splanchnic
- Splenic capillary hemangiomatosis.

2-.Primary increased resistance:

I. Prehepatic
- Thrombosis/cavernous transformation of the portal vein
- Splenic vein thrombosis

II. Intrahepatic

a-Presinusoidal
- Schistosomiasis
- Sarcoidosis
- Myeloproliferative disease and myelofibrosis
- Systemic mastocytosis
- Congenital hepatic fibrosis
- Idiopathic portal hypertension (hepatoportal sclerosis)
- Chronic arsenic hepatotoxicity
- Azathioprine hepatotoxicity
- Vinyl chloride hepatotoxicity
- Early primary biliary cirrhosis
- Early primary sclerosis cholangitis
- Partial nodular transformation
- Systemic mastocytosis

b.Sinusoidal/mixed
- Cirrhosis secondary to chronic hepatitis
- Alcoholic cirrhosis
- Cryptogenic cirrhosis
- Methotrexate
- Alcoholic hepatitis
- Hypervitaminosis A
- Incomplete septal fibrosis
- Nodular focal hyperplasia

c.Postsinusoidal:
- Veno-occlusive disease
- Hepatic vein thrombosis (Budd-Chiari syndrome)

III. Post-hepatic
- Inferior vena caval web
- Constrictive pericarditis
- Tricuspid regurgitation
- Severe right-sided heart failure

(Nathan et al., 2002).

1- Primary increased flow

- ***Arterial-portal venous fistula***

Hepatic arterial venous fistulae are abnormal communications between the hepatic artery and portal or hepatic vein and commonly occur either secondary to iatrogenic causes like liver biopsy, transhepatic biliary drainage, transhepatic cholangiogram and surgery, or following mechanical insult like blunt or penetrating trauma. Congenital fistulae are rare ***(Kumar et al., 2012).***

- ***Splenic capillary hemangiomatosis***

The spleen is mainly affected by benign tumors that originate from the vascular endothelium. The most common is hemangioma, which presents as small localized lesion. Isolated diffuse hemangiomatosis of the spleen is a rare entity in which the entire splenic parenchyma is replaced by a proliferation of neoplastic blood vessels ***(Ambrosio et al., 2012).***

2-Primary increased resistance

I- Prehepatic:

a- Portal venous thrombosis or obstruction:

- **Infection:**

Septicemia is the commonest cause as well as the umbilical vein infection in neonates for portal vein thrombosis. Acute appendicitis and peritonitis are causative factors in older children.

Ulcerative colitis and crohn's disease associated with infection can be complicated by portal vein block. Portal vein obstruction may be secondary to biliary infection due to gall stones and primary sclerosing cholangitis ***(Valla and Condat, 2000).***

- **Postoperative:**

The portal and splenic veins commonly block after splenectomy especially when, preoperatively, the patient had normal platelet count which rises postoperatively. The thrombosis spreads from the splenic vein into the main portal vein ***(Valla and Condat, 2000).***

- **Trauma:**

Portal vein injury usually follows automobile accidents or stabbing but portal vein injury is usually rare ***(Sherlock and Dooley, 2002).***

- **Hypercoagulable states:**

Myeloproleferative diseases especially polycythemia rubra vera are commonest associates. Hereditary protein C deficiency can be complicated by portal vein thrombosis ***(Denninger et al., 2000).***

- **Invasion and compression:**

The classic example is hepatocellular carcinoma. Carcinoma of pancreas, usually of the body, and of other adjacent organs may lead to portal vein block ***(Sherlock and Dooley, 2002).***

- **Congenital:**

Congenital absence of the portal vein (CAPV) with an extrahepatic portosystemic shunt is a rare malformation ***(Matsuura et al., 2010).***

- **Miscellaneous:**

Portal vein thrombosis has very rarely been associated with pregnancy and with oral contraceptive, especially in older women and with long usage. It also may be associated with thrombophlebitis migrans ***(Denninger et al., 2000).***

- **Unknown:**

In about half of the patients the etiology even after full investigations remain obscure. Some of these patients have associated autoimmune disorders such as thyroiditis, diabetes or rheumatoid arthritis ***(Sherlock and Dooley, 2002).***

b- Splenic vein thrombosis:

Isolated splenic vein thrombosis is a rare clinical syndrome that causes left-sided portal hypertension. It may lead to bleeding from gastric varices. The majority of splenic vein thrombosis are the result of pancreatic pathologies, including acute and chronic pancreatitis, pancreatic pseudocyst, pancreatic tumor and abscesses ***(Smith and Brand, 2001).***

II- Intrahepatic:

a) Presinusoidal

- **Schistosomiasis:**

Schistosomiasis is a major cause of portal hypertension and bleeding esophageal varices. The adult worms shed their eggs into the portal vein, and the eggs stop in the portal venules. The presence of the eggs results in granuloma formation, periportal fibrosis and obstruction of intrahepatic branches of the portal vein by fibrotic tissue ***(Bosch et al., 2003).***

- **Congenital hepatic fibrosis:**

The portal hypertension is probably due to deficiency of terminal branches of the portal vein in the fibrotic portal zones ***(Sherlock and Dooley, 2002).***

- **Myeloproliferative disease:**

The portal hypertension has been reported with myelofibrosis and chronic myeloid leukemia. The mechanism is related to infiltration of the portal zones with haemopoietic tissue, but thrombotic lesions in major and minor portal vein radicals and nodular regenerative hyperplesia contribute ***(Nathan and Francis, 2002).***

- **Systemic mastocytosis:**

The mast cell originates from the pluripotent "cluster of differentiation" (CD)-34-positive haematopoietic stem cell ***(Metcalfe, 2008).*** Mastocytosis is characterized by an abnormal

proliferation of mast cells, which accumulate in one or several organ systems, primarily in the skin and bone marrow. The disease is clinically heterogeneous and varies from a relatively benign condition with isolated cutaneous lesions to a very aggressive systemic condition with a grave prognosis. Mastocytosis is rare. In a Spanish paper, the incidence has been estimated to two cases per 100.000/year, but presumably the condition is under-diagnosed ***(Hagglund et al., 2008).***

Symptoms caused by non-cutaneous manifestations will most often originate from bone marrow, gastrointestinal tract, lymph nodes, liver, spleen, bones and the urogenital system. Accordingly, the following can be encountered: anemia, thrombocytopenia, malabsorption, hepato- and splenomegaly and bone disease in the form of lytic lesions and pathological fractures. These symptoms, which are all results of organ infiltration with secondary organ dysfunction, are termed C-findings ***(Castells and Austen, 2002).***

Portal hypertension is related to increase intrahepatic resistance secondary to mast cell infiltration. Increased splenic flow, perhaps with splenic arteriovenous shunting with histamine release may contribute ***(Sherlock and Dooley, 2002).***

- **Primary biliary cirrhosis:**

Portal hypertension may be a presenting feature long before the development of the nodular regeneration characteristic of cirrhosis ***(Nathan and Francis, 2002).***