INTRODUCTION

Cirrhosis is associated with a hyperdynamic circulatory state characterized by marked arteriolar vasodilation, increased cardiac output and regional organ blood flows, these hemodynamic changes play a critical role in the pathogenesis of portal hypertension and its complication such as variceal hemorrhage which is a major cause of death in patients with liver cirrhosis, much still could be performed in clinical practice to reduce the risk for bleeding in cirrhotic patients and accurate predictive rules should be provided for early recognition of high-risk patients ***(Groszmann, 1994).***

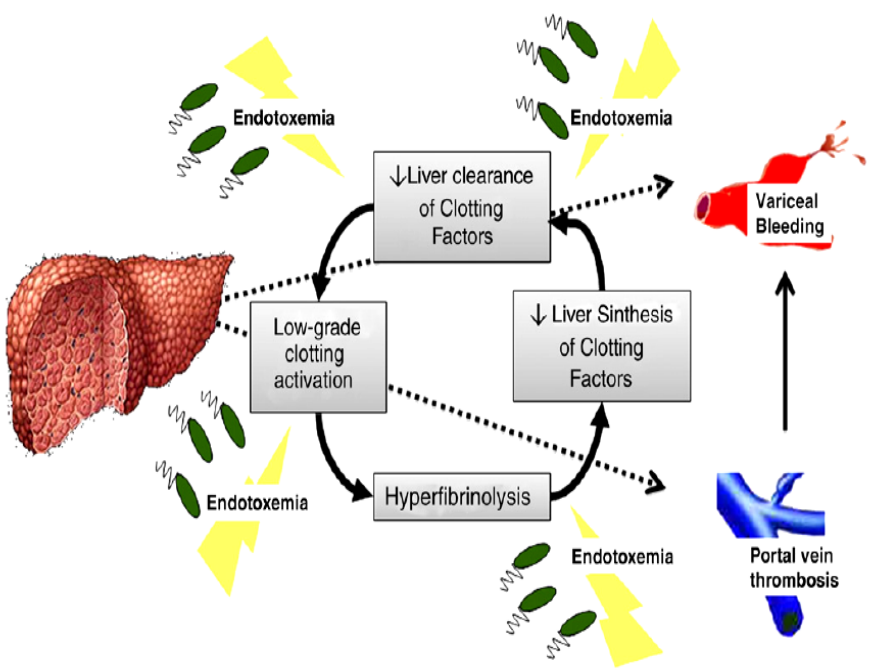

Figure (1): Haemostatic dysfunction in liver cirrhosis ***(European Journal of Internal Medicine 21, 2010)***

Endothelial dysfunction is an early key event in several vascular diseases and is considered one of the main mechanisms involved in the increased hepatic vascular tone of cirrhotic livers,Von-Willebrand factor is a surrogate marker of endothelial function that has been found increased in cirrhotic patients ***(Blann et al., 1993).***

vWF-Ag plays an important role in primary haemostasis and development of thrombotic vascular obliteration is discussed as a possible mechanism leading to portal hypertension, Von Willebrand Factor (vWF) is a glycoprotein synthesized predominantly by endothelial cells which is released in greater concentrations when these cells are damaged, therefore, vWF is increasingly recognized as a marker of endothelial cell activation, recent studies have demonstrated increased plasma levels of vWF in patients with cirrhosis, these experimental and clinical data suggest that impairment of endothelial-dependent factors might be a common finding in portal hypertension ***(Beer et al., 1998).***

Different stages of cirrhosis and subsequent portal hypertension can be evaluated precisely by hepatic venous pressure gradient (HVPG), however due to its invasiveness, only highly specialized centers perform HVPG-monitoring Of cirrhotic patient as standard algorithm, von Willebrand Factor Antigen (vWF-Ag) was thought to correlate well with HVPG in patients with liver cirrhosis, so Von Willebrand factor could be an index of endothelial dysfunction in patients with cirrhosis with a relationship to degree of Cirrhosis and portal hypertension ***(Ferro et al., 1996).***

AIM OF THE WORK

The aim of this study was to evaluate the relationship between plasma levels of Von Willebrand Factor (vWF) in patients with CLD due to infection with HCV at different stages of the disease.

Study aimed at exploring the correlation of this marker to systemic and hepatic hemodynamic and its possible relation to the development of cirrhosis and cirrhosis related events.

The study also aimed at exploring the expected relation between vWF-Ag and Hepatocellular Carcinoma, and the possibility to use vWF-Ag as a surrogate marker for HCC.

HEPATITIS C VIRUS

Introduction and epidemiology:

Hepatitis C virus (HCV) has been given many names, ‘the silent epidemic', ‘the silent dragon' and ‘the disease of the new millennium'. According to studies carried out by the World Health Organization approximately 170 million individuals (3% of the world's population) have been diagnosed with HCV. Chronic hepatitis C (CHC) is considered to account for about 70 to 75% of all cases of chronic hepatitis and 15-20% of all cases of cirrhosis of the liver and hepatocellular carcinoma ***(Thomas et al., 2010).***

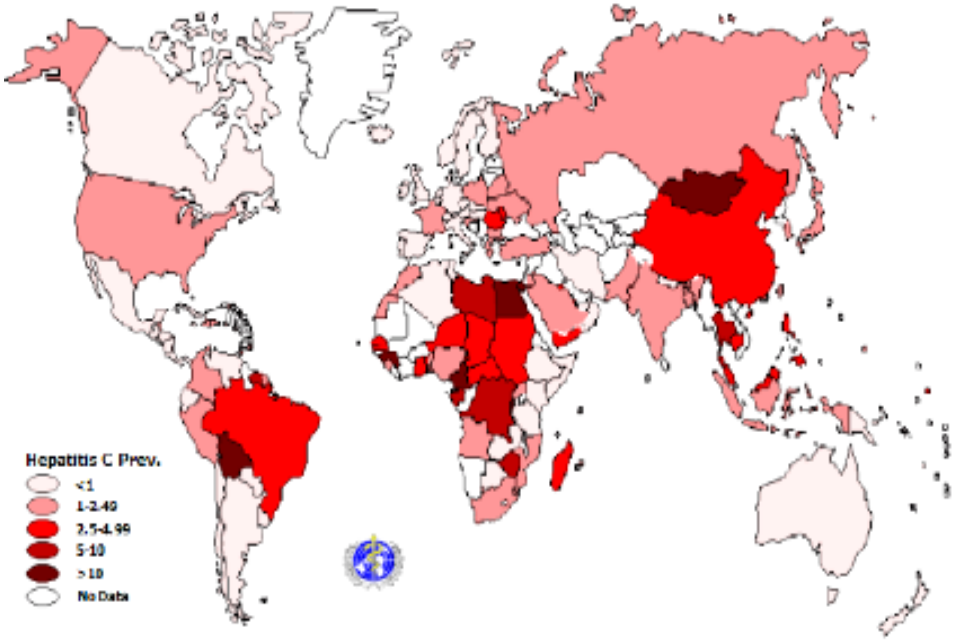

Figure (2): Global prevalence of hepatitis C
(World Health Organization, 2010)

Egypt has a very high prevalence of HCV and a high morbidity and mortality from chronic liver disease, cirrhosis, and hepatocellular carcinoma. Approximately 20% of Egyptian blood donors are anti-HCV positive. Egypt has higher rates of HCV than neighboring countries as well as other countries in the world with comparable socioeconomic conditions and hygienic standards for invasive medical, dental, or paramedical procedures. The strong homogeneity of HCV subtypes found in Egypt (mostly 4a) suggests an epidemic spread of HCV. Since a history of injection treatment has been implicated as a risk factor for HCV, a prime candidate to explain the high prevalence of HCV in Egypt is the past practice of parenteral therapy for schistosomiasis. The large reservoir of chronic HCV infection established in the course of these campaigns remains likely to be responsible for the high prevalence of HCV morbidity and may be largely responsible for the continued endemic transmission of HCV in Egypt today ***(Lavanchy and McMahon, 2000).***

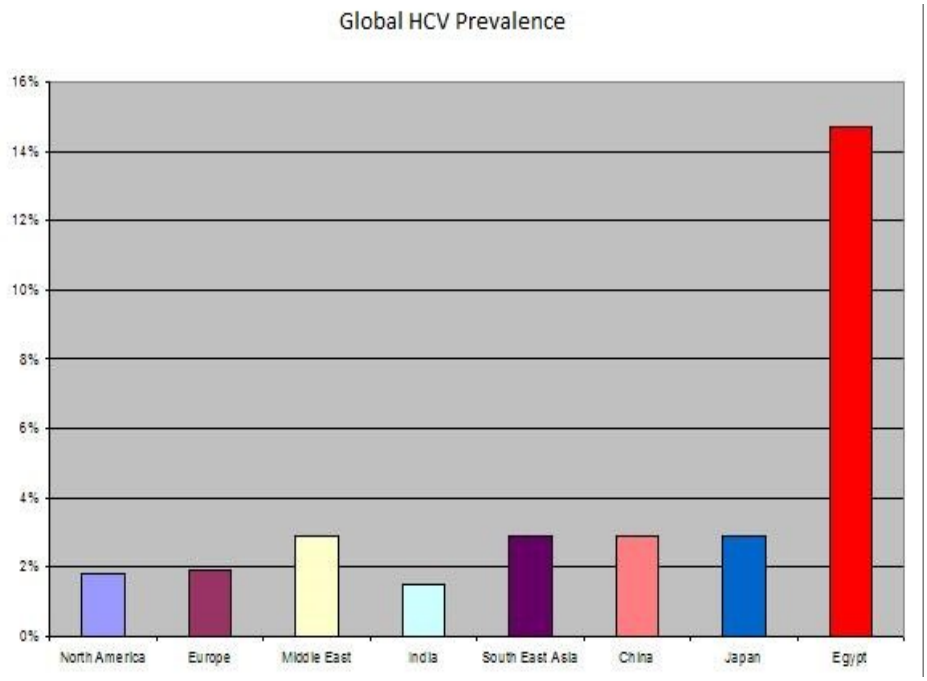

Figure (3): Global HCV prevalence ***(El-Zanaty et al., 2009)***

Numerous studies have confirmed that Egypt's viral hepatitis epidemic, particularly with regards to HCV, originated in the 1960s and 1970s during a mass campaign of parenteral antischistomal therapy (PAT) using improperly sterilized glass syringes ***(Brian and Maegraight, 1984).***

In 1918, it was discovered that "tartar emetic" (potassium antimony tartrate) could cure the infection, and between 1964 and 1982, over 2 million antimony injections were given per year to an average of 250,000 patients. The treatment campaign peaked between 1966 and 1969, when over 3 million doses were given annually ***(Mostafa, 2004).***

The connection between PAT and HCV has been proven by studies demonstrating the positive correlation between exposure to PAT and risk of HCV infection, the overlapping geographic distribution of HCV and Schistosomiasis infection in the country, and genotype tracing of HCV in Egypt ***(Naglaa, 2005).***

Viral hepatitis is arguably the most significant public health problem facing Egypt today. HCV prevalence rates in the general population are estimated at between 10% and 15% in rural areas, with some age groups suffering from prevalence rates of up to 50%. Incidence rates are estimated at 2-6 per 1,000 per year, a level that will maintain prevalence rates of 5-15% for the foreseeable future. The virus continues to be transmitted in medical and paramedical settings, as well as within communities and families. Approximately 5-7 million Egyptians carry antibodies for HCV and 3.3 million are chronically infected with HBV. Though not all persons infected with HBV and HCV proceed to develop cirrhosis of the liver or other life-threatening sequellae, the medical and economic burden incurred by those who do is significant. Liver disease is a top cause of mortality in Egypt, and mathematical models predict an upsurge in cases of liver cirrhosis and liver cancer in the years to come ***(Darwish et al., 1996).***

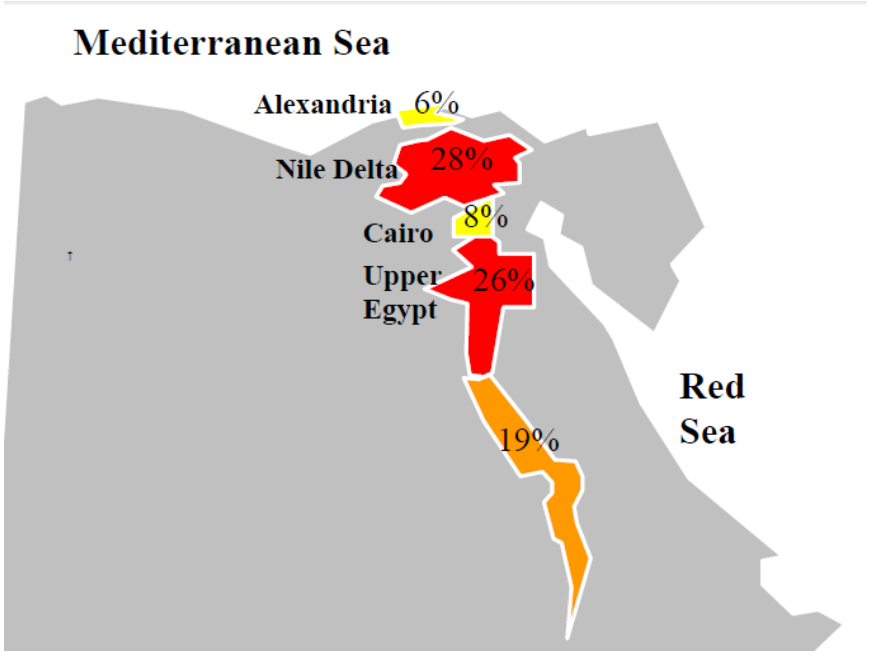

Figure (4): Age-adjusted prevalences of antibody to HCV for the population between 10 and 50 years of age ***(National survey, MOHP, 1996/7)***

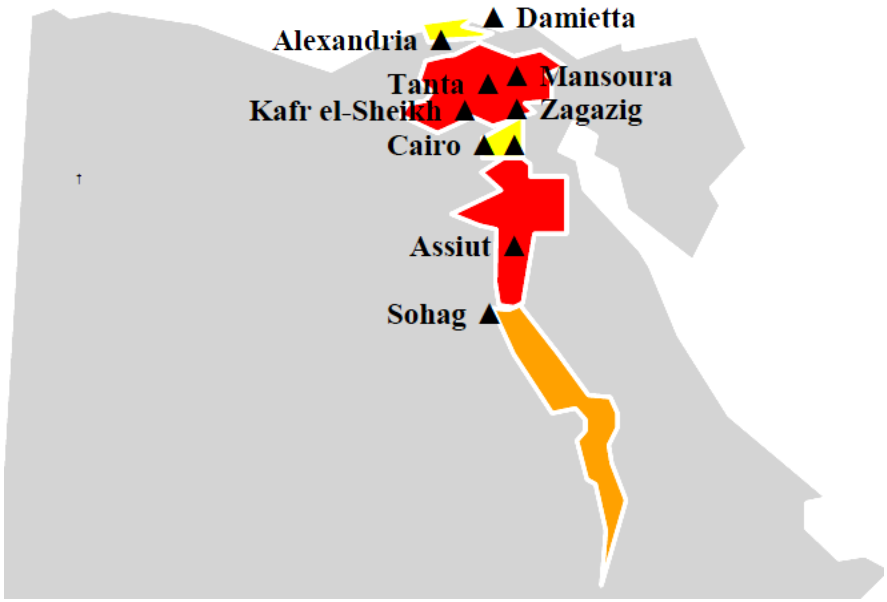

Figure (5): National Treatment Reference Centers open in Egypt ***(National, 2009)***

Genotype and Geography:

Hepatitis C virus (HCV), a member of the *Flaviviridae* family of RNA viruses, is characterized by genetic heterogeneity. At least 6 major HCV genotypes are identified. Each genotype differs from the others by 30%-35% of its nucleotide site sequence and also exists as numerous genetically distinct isolates ***(NIH, 2002).***

Each HCV genotype is unique with respect to its nucleotide sequence, geographic distribution, and response to therapy. Thus, each genotype can be considered a phylogenetically distinct entity requiring its own specific clinical appreciation. Knowledge of the epidemiology of HCV genotypes is essential not only for epidemiological reasons but also from a clinical standpoint. The infecting HCV strain is known to be one of the main independent factors that influence the outcome of antiviral therapy ***(Hnatyszyn, 2005).***

Genotypes 1, 2, and 3 are common throughout the United States and Europe ***(Robertson et al., 1998)*** and have thus become the focus of much interest and research. The clinical presentation and management of infections arising from these viral genotypes has advanced rapidly. In contrast, genotypes 4, 5, and 6 have not been adequately studied; therefore, the management strategies for patients infected with these genotypes are not as well developed ***(WHO, 2007).***

HCV genotype 4 (HCV-4) is common in the Middle East and in Africa, where it is responsible for more than 80% of HCV infections, and has recently spread to several European countries ***(Nguyen and Keeffe, 2005).***

Egypt has the highest prevalence of HCV worldwide (15%) and the highest prevalence of HCV-4, which is responsible for almost 90% of infections and is considered a major cause of chronic hepatitis, liver cirrhosis, hepatocellular carcinoma, and liver transplantation in the country ***(Egyptian Ministry of Health Annual Report, 2007).***

Although HCV-4 is the cause of approximately 20% of the 170 million cases of chronic hepatitis C in the world, it has simply not been the subject of widespread research; therefore, the features of this genotype and management strategies for patients infected with this genotype are not as well developed as for genotypes 1, 2, and 3 ***(Abdel Aziz et al., 2000).***

Egypt has the largest epidemic of Hepatitis C virus in the world, the overall prevalence positive for HCV ab in Egypt was 14.7%, 9.8% of the population continue to have HCV RNA, this means that 7.8 millions of the egyptians continue to have chronic active hepatitis (according to Egyptian demographic healthy survey) ***(Kamel et al., 1992).***

Transmission:

There are several possible modes of transmission, including nosocomial procedures, parenteral transmission and vertical transmission (from mother to baby during pregnancy or birth).

1- Nosocomial:

Nosocomial procedures are likely the leading source of HCV transmissions worldwide and are also responsible for a large percentage of HBV infections. Health workers are at risk of infection by both viruses, particularly in settings where prevalence rates are high. Transmission of HCV occurs after 2-8% of accidental needle stick exposure, the rate significantly higher for HBV (about 30%) ***(Thomas and Lemon).***

2- Parenteral:

Hepatitis c is transmitted by blood transfer, most people will not be symptomatic during the acute infection but approximetly 70% will remain infected, chronic infections carry a substantial risk of liver damage, cirrhosis and liver cancer. A particular risk are people who had blood transfusion prior to the introduction of screening of blood products for hepatitis C in 1992 and people who inject street drugs for share needles ***(Law and Rudnicka, 2006).***

Table (1): Prevalence of HBV, HCV in MOHP and non-MOHP donors after screening

	HBs Ag	**Anti HCV**
National Blood Transfusion Center (NBTC) blood	1.2%	5.0%
Non-NBTC blood	1.4%	7.6%

(MOHP and NBTC, 2007)

Even in countries where the blood supply is screened for viral hepatitis, the risk for parenteral infection can be significant, as injections may be performed with inadequately sterilized equipment. Indeed the WHO estimates the unsafe injections for 2 million new HCV infections and 21 million new HBV infections worldwide in 2000 ***(Anja et al., 2004).***

Exposure may be multiplied by the frequent practice of non medical settings for example; family members injections, traditional healers, barbering, tattoos, body piercing. Although other medical procedures such as dialysis, transplantation, obstetrical and dental procedures, also transmit the viruses if equipment is not properly sterilized ***(Souto et al., 2012).***

3- Vertical:

Perinatal transmission also occurs in 2.7-8.4% of infants born to mothers positive for anti-HCV, and more frequently when mothers are also HIV-positive ***(Colin et al., 2005).***

A recently study of intra-familial transmission showed that the incidence of offsprings to acquire HCV from anti-HCV positive parents is slightly higher (about 8.7/1000 per year) in the positive mothers than in the positive fathers (6.6/1000 per year) ***(Mohamed et al., 2005).***

4- Sexual:

Sexual transmission of HCV is much rare- seronegative sexual partner of HCV-positive people rarely become infected, even after years of cohabitation. This is likely due to the much lesser infectivity of HCV compared to HBV. In addition, certain subpopulations with recognized frequent, multipartner sexual activity, such as professional sex workers (prostitutes), promiscuous homosexualmen, and persons of both sexes attending clinics for sexually transmitted diseases, have a higher frequency of serologic markers of HCV infection than the general population ***(Alter et al., 1990).***

Comment on transmission:

Although blood transfusion, circumcision, vertical transmission, and living in a house with an infected family member are the established risk factors for HCV transmission, they have not been recorded in more than 20% of diagnosed patients, and approximately 70% of acquired infections are due to unindentified risk factors ***(Habib et al., 2001).***

So this means that multiple exposure to unsterilized needle pricks, razors or dental procedures are responsible for higher carrier rate in low socioeconomic groups ***(Hyder et al., 2001)***.

Table (2): Relative importance of various modes of transmission for HBV and HCV

		IDU	Nosocomial/ non- IDU parenteral	Sexual	Vertical/ early childhood
HBV	Developing countries	+	++	+	+++
	Western countries	+++	-	++	-
HCV	Developing countries	+	+++	?	+
	Western countries	+++	+	+	-

(Thomas and Lemon)

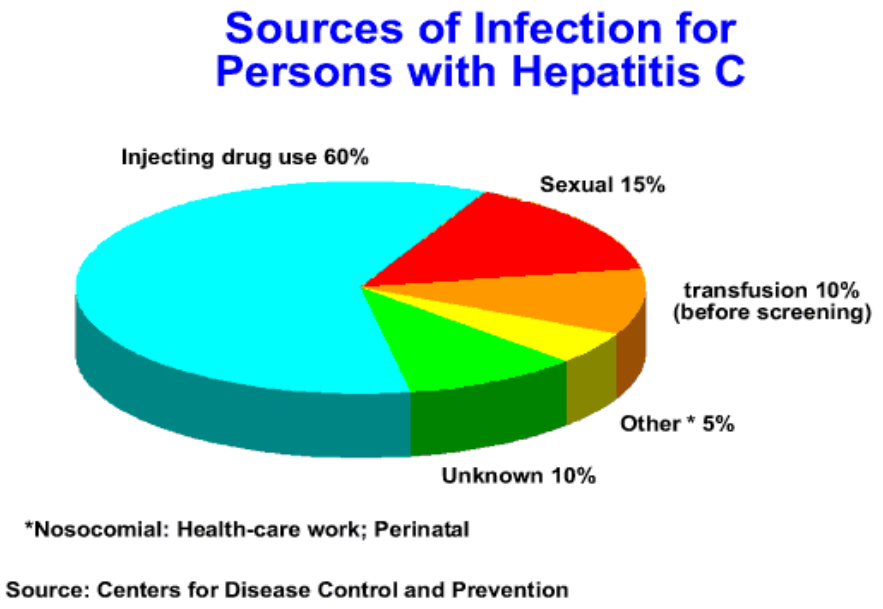

Figure (6): Sources of infection for persons with hepatitis C ***(www.cdc.gov/hepatitis/hcv/)***

Acute infection:

Acute HCV infection is asymptomatic in 50-90% of cases. Failure to spontaneously eradicate infection occurs in 50-90% of cases according to the route of transmission, the presence of symptomatic hepatitis, and to the age at which infection occurred ***(Santantonio et al., 2008)***.

Chronicity and prognosis:

Chronic infection is associated with variable degrees of hepatic inflammation and fibrosis progression, regardless of HCV genotype and of viral load.

Only exceptionally cases do resolve spontaneously. Liver disease progression takes place over several decades, and is accelerated in the presence of cofactors such ad alcohol consumption, diabetes mellitus (to which HCV itself appears to predispose), older age of acquisition, human immunodeficiency virus (HIV) co infection, or co infection with other hepatotropic viruses ***(Afdhal, 2004)***.

Depending on the presence of co-factors, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Death related to the complications of cirrhosis may occur, at an incidence of approximately 4% per year, whereas HCC occurs in this population at an estimated incidence of 1-5% per year ***(Thompson et al., 2007)***. Patients diagnosed with HCC have a 33% probability of death during the first year ***(Yang and Roberts, 2010)***.