Introduction

Hepatitis C is a major global public health problem, it is an infectious disease affecting primarily the liver, this infection is often asymptomatic but chronic infection leads to scaring of the liver and liver failure, liver cancer or life threatening esophageal and gastric varices ***(Ryan et al., 2004).***

Egypt has a very high prevalence of HCV and a high morbidity from chronic liver disease, cirrohsis, hepatocellular carcinoma. Aproximatly 20% of Egyptian blood donors are anti-HCV positive ***(El-Zeyadi et al., 2005; Strick Land et al., 2002)***.

The strong homogeneity of HCV subtypes found in Egypt (mostly genotype A4), suggest an epidemic spread of HCV aprime candidate to explain the high prevalence of HCV in Egypt is the past practice of paraenteral therapy for schistosomiasis and largely responsible for the continued endemic trasnsmision of HCV in Egypt today, where it is infects about 15% of the general population ***(Holmbeg et al., 2012).***

The aim of the treatment of chronic hepatitis is to reduce inflammation to prevent progression to fibrosis, cirrhosis and hepatocellular carcinoma and to decrease infectivity and control the spread of the disease ***(World health organization, Global surveillance and control of hepatitis C, 1999).***

The treatment of choice for chronic Hepatitis C is the combination therapy of the Interferon with Ribavirin for 48 weeks. Response to treatment vary according the genotype of the virus, sustained response is about 40-50% in people with HCV genotype 1given 48 weeks of treatment, 70-80% of people with genotype 2and 3 with 24 weeks of treatment, and 65% in those with genotype 4 given 48 weeks of treatment ***(Rosen et al., 2011).***

Non responder are defined as failure to clear HCV RNA from serum after 24 weeks of therapy that may be due to interrupted treatment, stoppage of treatment due to any cause, highly resistant genotype of HCV and Sustained Virological Response means HCV RNA become negative 24 weeks after cessation of treatment ***(Khattab, 2009).***

Vitamin D is a fat soluble vitamins that is naturally present in few foods as fatty fish species, eggs, beef liver fish, and ultraviolet irrigated mushromes and yeast and available as a dietary supplement. it is produced endogenously when ultraviolet rays strik the skin and trigger vitamin D synthesis, that about 10% of vitamin D is from the food and about 90% of vitamin D is synthatized endogenousy ***(Institute of Medicine; Food and Nutrition Board; National Academy Press, 2010).***

Vitamin D is considered as prohormone and by two hydroxylation the first one in the liver and called calcidol (OH) vit D that converted to calcitrol 1,25(OH)2, calcitrol acts locally as acytokines defending the body against microbial

invade, vitamin D increase Calcium and Phsphate absorption from the intestine and promote normal bone formation and mineralization and prevent hypocalcimec tetany ***(Adams et al., 2010).***

Recently vitamin D regulate the expression of over 200 different genes and affect in treatment of asthma, Type-1 diabetes mellitus, cardiovascular diseases and decrease the risk of developing multiple sclerosis and risk of cancers these effects may be secondary to both local production of calcitrol and it is autocrine and parocrine action on cellular proliferation and diferntioation, apoptosis, insulin and rennin secretion, interleukin and bacterial proteins production through calcium regulating dependant process ***(Holick et al., 2007).***

The prevalence of vitamin D insuffecincy has been estimated to range from aminimum of about 50% to amaximum of perhaps 75% or greater ***(Gorden et al., 2008).***

There is relationship between vitamin D and other liver diseases, in the view of bile acid dependant uptake of vitamin D and its hepatic metabolism its responsible to expect an association between vitamin D status and both cholestatic and non cholestatic chronic liver disease and serum cocenteration of 1,25 $(OH)_2$ vitamin D, they decrease in patients with cirrohsis versus non cirrhotic patients ***(Southern et al., 2010; Fisher et al., 2007)***.

Recently a significant correlation between 25 (OH) vitamin D level and stage of fibrosis because vitamin D has antifibrinogenic effect and anti inflammatory effect so with lower 25 (OH) vitamin D the stage of fibrosis is increased and severity of necroinflammatory activity was observed, so low vitamin D is linked to severe fibrosis and low sustained virological response on interferon therapy and increase the risk of side effect of interferon ***(Abu Mouch et al., 2011).***

Vitamin D supplementation was reported to improve the probability of achiving sustained virological response when combined with antiviral treatment against hepatitis C virus (HCV) and decrease HCV infectous virus production and vitamin D is an immune modulator that has adirect effect on T. cells and antigens presenting immune cells and can directly and indirectly influence the differentiation and activity of CD4 T. cells ***(Schauber et al., 2007; Mahon et al., 2003).***

The Committee of the Institute of Medicine concluded that persons at risk of vitamin D deficiency at serum 25(OH) concentration <30nmol/L(12ng/ml).some people are potentially at risk for inadequacy at levels ranging from 30-50nmol/L(12-20ng/ml). practically all people are sufficient at levels >=50 nmol/L(>=20 ng/ml),the committee stated that 50nmol/L is the serum 25(OH)D level that covers the needs of 97.5% of the population. serum concentration >125 nmol/L (>50ng/ml) are associated with potential adverse effect.

Serum concentration of (OH)D is the best indicator of vitamin D status. it reflects vitamin D produced cutaneously and that obtained from food and supplements and has a fairly long circulating half-life of 15 days, but circulating $1,25(OH)_2$Dis generally not a good indicator of vitamin D status because it has a short half-life of 15 hours and serum concentration are closely regulated by parathyroid hormone, calcium, and phosphate ***(Carter, 2009).***

Aim of the Work

1. Assess the vitamin D status among group of patients candidates for interferon therapy.
2. Study the interelationship between vitamin D status and the response to antiviral therapy.

Chapter one

Hepatitis C

Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus *(HCV)*. The infection is often asymptomatic, but chronic infection can lead to scarring of the liver and ultimately to cirrhosis, which is generally apparent after many years. In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life-threatening esophageal and gastric varices ***(Georgel.,et al 2010)***

HCV is spread primarily by blood-to-blood contact associated with intravenous drug use, poorly sterilized medical equipment and transfusions. An estimated 130–170 million people worldwide are infected with hepatitis C. The existence of hepatitis C (originally "non-A non-B hepatitis") was postulated in the 1970s and proven in 1989. It is not known to cause disease in other animals ***(Houghton, 2009).***

The virus persists in the liver in about 85% of those infected. This persistent infection can be treated with medication; pegelated interferon and ribavirin are the current standard therapy. Overall, between 50–80% of people treated are cured. Those who develop cirrhosis or liver cancer may require a liver transplant. Hepatitis C is the leading cause of liver transplantation though the virus usually recurs after transplantation. No vaccine against hepatitis C is currently available ***(Rosen, 2011).***

Signs and symptoms:

Acute infection:

Hepatitis C infection causes acute symptoms in 15% of cases ***(Maheshwari et al., 2008).*** Symptoms are generally mild and vague, including a decreased appetite, fatigue, nausea, muscle or joint pains, and weight loss ***(Wilkis et al., 2010).*** Most cases of acute infection are not associated with jaundice. The infection resolves spontaneously in 10-50% of cases, which occurs more frequently in individuals who are young and female.

Chronic infection:

About 80% of those exposed to the virus develop a chronic infection ***(Nelson et al., 2011).*** Most experience minimal or no symptoms during the initial few decades of the infection although chronic hepatitis C can be associated with fatigue. Hepatitis C after many years becomes the primary cause of cirrhosis, and liver cancer, About 10–30% of people develop cirrhosis over 30 years, Cirrhosis is more common in those co infected with hepatitis B or HIV, alcoholics, and those of male gender. Those who develop cirrhosis have a 20 fold greater risk of hepatocellular carcinoma, a rate of 1-3% per year. and if this is complicated by excess alcohol the risk becomes 100 fold greater ***(Muller et al., 2009).*** Hepatitis C is the cause of 27% of cirrhosis cases and 25% of hepatocellular carcinoma worldwide ***(Alter, 2007).***

Liver cirrhosis may lead to portal hypertension, ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, varices (enlarged veins, especially in the stomach and esophagus), jaundice, and a syndrome of cognitive impairment known as hepatic encephalopathy. It is a common cause for requiring a liver transplant ***(Ozaras and Tahan, 2009).***

Extra hepatic Manifestations:

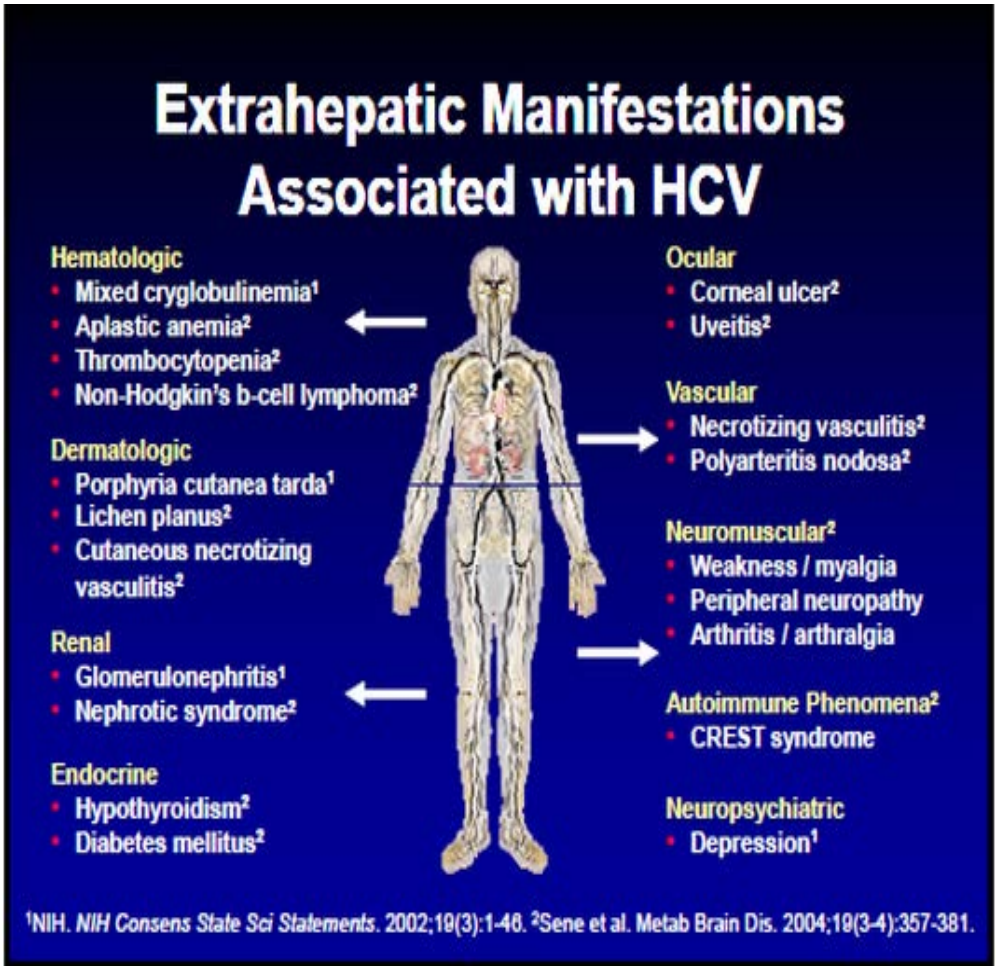

Figure (1): Extrahepatic maifestation associated with HCV

Hepatitis C is also rarely associated with Sjögren's syndrome (an autoimmune disorder), thrombocytopenia, lichen planus, diabetes mellitus, and B-cell lymphoproliferative disorders ***(Zignego et al., 2007).*** Thrombocytopenia is estimated to occur in 0.16% to 45.4% of people with chronic hepatitis C ***(Louie et al., 2011).*** Putative associations with Hyde's prurigo nodularis ***(Lee and Shunack, 2005)*** and membranoproliferative glomerulonephritis have been reported.

Virology:

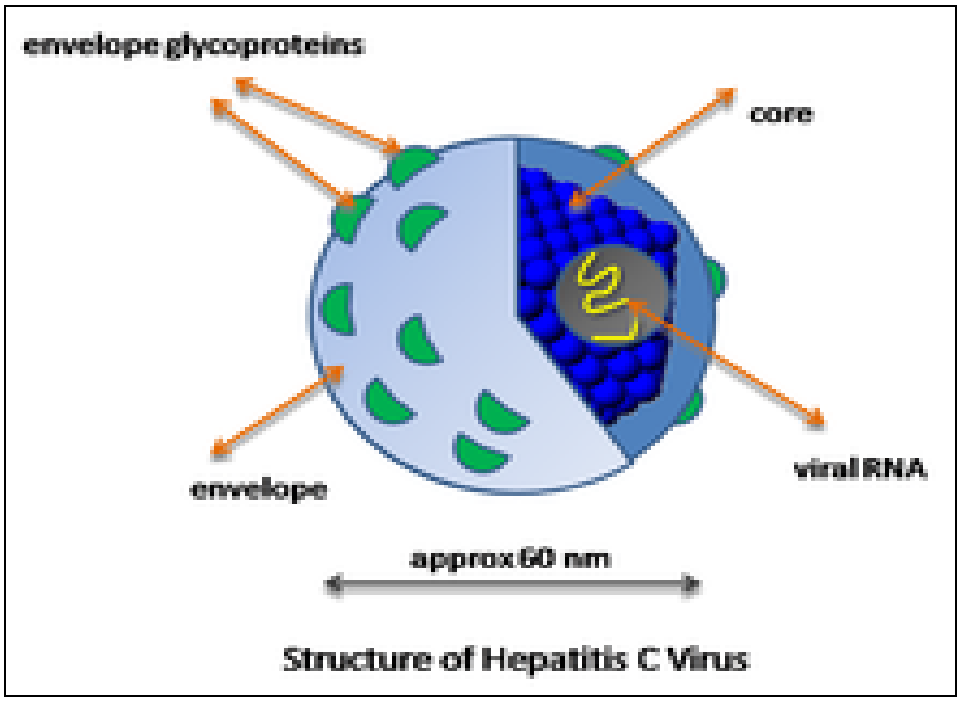

Figure (2): Structure of HCV.

Table (1): Regional distribution of HCV genotyping.

Region	Predominant HCV genotype
Europe, North America, Japan	Genotype 1a, 1b (genotypes 2 & 3 are less common)
Southeast Asia	Genotype 3
Egypt, the Middle East, Central Africa	Genotype 4
South Africa	Genotype 5
Asia	Genotype 6

The hepatitis C virus (HCV) is a small, enveloped, single-stranded, positive-sense RNA virus. It is a member of the hepacivirus genus in the family Flaviviridae There are seven major genotypes of HCV, which are indicated numerically from one to seven ***(Nakano et al., 2011).*** In the United States, about 70% of cases are caused by genotype 1, 20% by genotype 2, and about 1% by each of the other genotypes Genotype 1 is also the most common in South America and Europe. In Egypt the most common genotype 4 that cause more than 80% of hepatitis C in Egypt. In Euorpe the most common genotype 2 & 3 ***(Pawlotsky et al., 1995).***

Transmission:

The primary methods of transmission in the developed world is intravenous drug use (IDU), while in the developing world the main methods are blood transfusions and unsafe

medical procedures ***(Maheshwari and Thulvath, 2010).*** The cause of transmission remains unknown in 20% of cases ***(Ponde and Mikhailova, 2011).***

Intravenous drug use:

IDU is a major risk factor for hepatitis C in many parts of the world ***(Xia et al., 2008).*** Of a review of 77 countries 25 had rates of hepatitis C in the intravenous drug user population of between 60% and 80% including the United States, and China. While twelve countries had rates greater than 80%. It is believed that ten million intravenous drug users are infected with hepatitis C; China (1.6 million), the United States (1.5 million), and Russia (1.3 million) have the highest absolute totals. Rates of hepatitis C among prison inmates in the United States are ten to 20 times that of the rates of the general population, which is attributed to high-risk behavior such as IDU and tattooing with nonsterile equipment ***(Vescio et al., 2008; Imperial, 2010).***

Healthcare exposure:

Blood transfusion, blood products, or organ transplantation without HCV screening is a significant risk for infection. The United States instituted universal screening in 1992 and the risk subsequently has decreased to one in 10,000 to 10,000,000 per units of blood down from a risk of one in 200 units of blood ***(Ponde and Mikhailova, 2011).***

This low risk remains as there is a period of about 11–70 days between the potential blood donor acquiring hepatitis C and their blood testing positive depending on the method. Some countries still do not screen for hepatitis C due to the cost.

Hospital equipment has also been documented as a method of transmission of hepatitis C including: reuse of needles and syringes, multiple-use medication vials, infusion bags, and improperly sterilized surgical equipment, among others. Limitations in the implementation and enforcement of stringent standard precautions in public and private medical and dental facilities are known to be the primary cause of the spread of HCV in Egypt, the country with highest rate of infection in the world ***(Alter, 2007)***.

Sexual intercourse:

Whether hepatitis C can be transmitted through sexual activity is controversial ***(Tohne and Holmberg, 2010).*** While there is an association between high-risk sexual activity and hepatitis C, when there is a concurrent sexually transmitted infection, including HIV or genital ulceration.

Body piercing:

Tattooing is associated with two to threefold increased risk of hepatitis C. This can be due to either improperly sterilized equipment or contamination of the dyes being used, Tattoos or piercing performed either before the mid-1980s, "underground," or nonprofessionally are of particular for tattoos in a licensed facility to be directly associated with HCV infection ***(Jafari et al., 2010)***.

Shared personal care items:

Concern, since sterile techniques in such settings may be lacking. The risk also appears to be greater for larger tattoos It is estimated that nearly half of prison inmates share unsterilized tattooing equipment. It is rare Personal-care items such as razors, toothbrushes, and manicuring or Pedi curing equipment can be contaminated with blood. Sharing such items can potentially lead to exposure to HCV ***(Lack et al, 2006).***

Appropriate caution should be taken regarding any medical condition that results in bleeding, such as cuts and sores. HCV is not spread through casual contact, such as hugging, kissing, or sharing eating or cooking utensils.

Vertical transmission:

Vertical transmission of hepatitis C from an infected mother to her child occurs in less than 10% of pregnancies. There are no measures that alter this risk ***(Lam et al., 2010).*** It is not clear when during pregnancy transmission occurs, but it may occur both during gestation and at delivery A long labor is associated with a greater risk of transmission. There is no evidence that breast-feeding spreads HCV; however, to be cautious, an infected mother is advised to avoid breastfeeding if her nipples are cracked and bleeding or her viral loads are high ***(Mast, 2004).***

Diagnosis:

Table (2): Diagnostics: acvte, cleared, or chronic HCV

Diagnosis:	Prior, cleared HCV infection	Acute HCV infection	Chronic HCV infection
Antibody Test	Positive	Negative; becomes positive within 6 to 24 weeks	Positive
Viral Load Test (HCV RNA)	Undetectable on two tests, performed at least six months apart	Detectable within 1 to 2 weeks, usually very high	Detectable
ALT Test (Alanine Aminotransferase, a liver enzyme)	May be normal, fluctuate, or be persistently raised	May be up to 7 to 10 times above the normal level	May be persistently normal, fluctuate, or be persistently raised

There are a number of diagnostic tests for hepatitis C including: HCV antibody enzyme immunoassay or ELISA, recombinant immunoblot assay, and quantitative HCV RNA polymerase chain reaction (PCR). HCV RNA can be detected by PCR typically one to two weeks after infection, while antibodies can take substantially longer to form and thus be detected ***(Ozaras and Tahan, 2009).***

Chronic hepatitis C is defined as infection with the hepatitis C virus persisting for more than six months based on the presence of its RNA Chronic infections are typically without symptomatic during the first few decades, and thus it is most commonly discovered following the investigation of elevated liver enzyme levels or during a routine screening of high risk individuals. Testing is not able to distinguish between acute and chronic infections.