INTRODUCTION

Hepatitis C is an infectious disease affecting primarily the liver, caused by hepatitis C virus (HCV). The infection is often asymptomatic, but chronic infection can lead ultimately to cirrhosis, which is generally apparent after many years ***(Di Tomaso et al., 2011)***.

In some cases, those with cirrhosis will go on to develop liver failure, liver cancer or life threatening esophageal and gastric varices ***(Di Tomaso et al., 2011)***.

Egypt has the largest epidemic of HCV in the world. The prevalence of HCV in Egypt is 14.7%. HCV infection persists in the liver in about 85% of those infected ***(Di Tomaso et al., 2011)***.

Interferon is the drug of choice for treatment of chronic HCV infection, Interferon (IFN) has immunomodulatory properties such as direct increase in production of pathogen auto-antibodies, enhanced cytotoxic T cell & B cell activities, inhibition of T suppressor cell function and induction of HLA class I antigen expression ***(Kasagi et al.,2009).***

PEGylation is a process whereby one or more molecules of polyethylene glycol (PEG) are covalently attached to a biological or small-molecule drug, with the goal of transforming it into a therapy with improved pharmacokinetic

and pharmacodynamic properties. In these formulation, PEG is added to make interferon last longer in the body, so Pegylated IFN is taken once per week while conventional Interferon is taken 3 times per week, so it improves the compliance of the patient ***(Dittmar et al., 2011).***

It is recorded that sustained viral response/cure rates are much better in Pegylated interferon plus Ribavirin (94%) than in those who received conventional interferon plus ribavirin (80%) ***(Sahin et al., 2009).***

Interferon induce autoimmune disorders including autoimmune thyroiditis, hemolytic anemia and thrombocytopenia, systemic lupus erythrematosis (SLE), rheumatoid arthritis and psoriasis, however, these autoimmune diseases except for autoimmune thyroiditis, are rare among side effects of IFN therapy ***(Ban et al., 2010)***.

The incidence of autoimmune thyroid disorder with Pegylated interferon is 6%, half of them completely cure with discontinuation of interferon (***Lucas et al., 2010).***

The principal biochemical characteristic of the autoimmune thyroid disorder is the presence of thyroid autoantibodies (TAbs) in the patient's serum against two major thyroid antigens, thyroid peroxidase (TPO) and thyroglobulin (Tg) ***(Brix et al., 2010).***

Antibodies against TPO (TPOAbs) and Tg (TgAbs) are of immunoglobulin G class, both showing high affinity for their respective antigens. Unlike TgAbs, TPOAbs can activate complement and are able to cause damage to thyroid cells due to antibody dependent cell cytotoxicity ***(Brix et al., 2010).***

In autoimmune thyroid diseases, TPOAbs are present in nearly all (>90 %) patients, while TgAbs can be detected in approximately 80% ***(Brix et al., 2010).***

Chemokine ligand 10 (CXCL10) is an IFN – γ inducible chemokine involved in the Th1 autoimmune response. In the autoimmune thyroid disease CXCL10 is involved in the recruitment of Th1 lymphocytes which secrete IFN – γ that in turn stimulates chemokine production by follicular cells, maintaining the autoimmune process. CXCL10 reflects the degree of autoimmune reaction and thyroid infilteration by inflammatory cells ***(De Freitas et al., 2010)***.

AIM OF THE WORK

This work aims to assess the incidence of autoimmune thyroid disorder following treatment of chronic HCV infection with Pegylated Interferon among Egyptian cases.

HEPATITIS C VIRUS

Histological Background:

Non-A, non-B hepatitis, currently named hepatitis C virus (HCV), had been described from more than two decades, and in that time considerable advancements had been made in the mapping of routes of viral transmission**.** The viral genome was molecularly cloned in1988 by Daniel W and Michael H and its organization was delineated shortly thereafter. However blood tests were not available until 1991, this means that its emergence as a global health issue went largely undetected at the time and that analysis of the pandemic is largely retrospective ***(Houghton, 2009).***

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 ***(Robertson et al., 2010).***

Hepatitis C Infection and Chronic Hepatitis C in Egypt:

The prevalence of HCV infection varies throughout the world, with the highest number of infections reported in Egypt.

The use of parenteral antischistosomal therapy in Egypt is thought to have contributed to a prevalence of antibodies against HCV in various regions. In the United States, 1.8 percent of the population is positive for HCV antibodies ***(Hnatyszyn, 2005)*** (Figure 1).

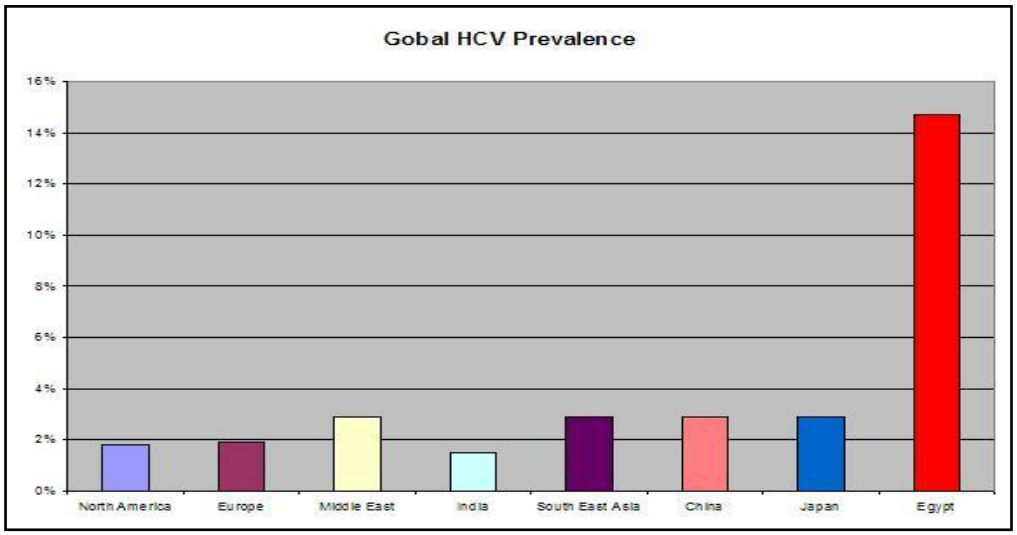

Figure (1): Worldwide prevalence of HCV ***(Perz et al., 2005).***

Egypt has a population of 83 million and contains the highest prevalence of hepatitis C in the world. The national prevalence rate of HCV antibody positivity has been estimated to be between 14-20%. This is ten times greater than in any other country in the world. The estimated adjusted national prevalence rate of chronic hepatitis C infection in Egypt is 7.8% or 7.3 million people in 2009. Only one third of these individuals (2.75 million) are estimated to have chronic liver disease (elevated ALT) and furthermore, among these one third

(825,000 people) are suffering from advanced liver disease ***(Kamal et al., 2010).***

The prevalence of HCV varies throughout the country. The available data suggests that the northern Nile Delta has the highest prevalence 28%. The much smaller population of Upper Egypt, in the south, has a slightly lower HCV prevalence 20%. The two major urban centers, Cairo and Alexandria, have the lowest prevalence of 9% and 6%, respectively ***(Abdel-Aziz et al., 2009).***

Epidemiological Character:

The factors most strongly associated with infection are injection-drug use and receipt of a blood transfusion before 1990 but in some cases no risk factors can be identified**.** Poverty, high-risk sexual behavior, are linked to an increased risk of infection, but the reasons for some of these associations remain unclear. Maternal–fetal transmission occurs but is infrequent and often associated with co-infection with HIV in the mother ***(Lauer and walker, 2001).***

Virus can be recovered from the saliva of infected persons and although chimpanzees have been experimentally infected by the injection of saliva from HCV-infected person, casual household contact and contact with the saliva of infected persons also appear to be very inefficient modes of

transmission. Hospital transmission has been documented, such as from patient to patient by a colonoscope, during dialysis and during surgery ***(WHO, 2007).***

Until relatively recently, blood transfusion posed a major risk of HCV infection in developed countries. The introduction in 1990 and 1992 of improved blood-screening measures based on the detection of HCV antibodies has dramatically decreased the risk of transfusion-associated HCV infection. The current risk in the United States from blood that is negative for HCV antibodies is less than 1 in 103,000 transfused units with the residual risk resulting from blood donations that occur in the interval between infection and the development of detectable antibodies (estimated to be less than 12 weeks) ***(Lanford et al., 2008).***

The risk associated with blood transfusion may now be even lower, since new screening methods, such as direct screening of pooled samples by polymerase-chain-reaction (PCR) assays should decrease the window period after infection to about three weeks ***(Nguye and Keeffe, 2005).***

Even though the prevalence of HCV infection is higher among health care workers than in the rest of the population, needle-stick injuries in the health care setting continue to result in nosocomial transmission of the virus. A rough estimate of the comparative risks of transmission through a needle stick is provided by the rule of threes: HBV is transmitted in 30 percent

of exposures, HCV in 3 percent, and HIV-1 in 0.3 percent. These numbers are most likely influenced by the size of the inoculum, the size of the needle, and the depth of inoculation ***(Njouom et al., 2007).***

Hepatitis C Phenotypes and Genotypes:

Hepatitis C virus is a spherical, enveloped, single-stranded RNA virus belonging to the Flaviviridae family and Flavivirus genus. In ***2001, Lauer and WaIker*** reported that HCV is closely related to dengue and yellow fever viruses. HCV can produce at least 10 trillion new viral particles each day. RNA-dependent RNA polymerase, an enzyme critical in HCV replication, lacks proofreading capabilities and generates a large number of mutant viruses known as quasispecies. These represent minor molecular variations with only 1% - 2% nucleotide heterogenicity. HCV quasispecies pose a major challenge to immune-mediated control of HCV and may explain the variable clinical course and the difficulties in vaccine development ***(Lauer and WaIker, 2001).***

The hepatitis C virus genome consists of a single, open reading frame and 2 untranslated, highly conserved regions, 5'-NTR and 3'-NTR, at both ends of the genome (Figure 2). The genome has approximately 9500 base pairs and encodes a single po1yprotein of 3011 amino acids that are processed into 10 structural and regulatory proteins ***(Houghton, 2009).***

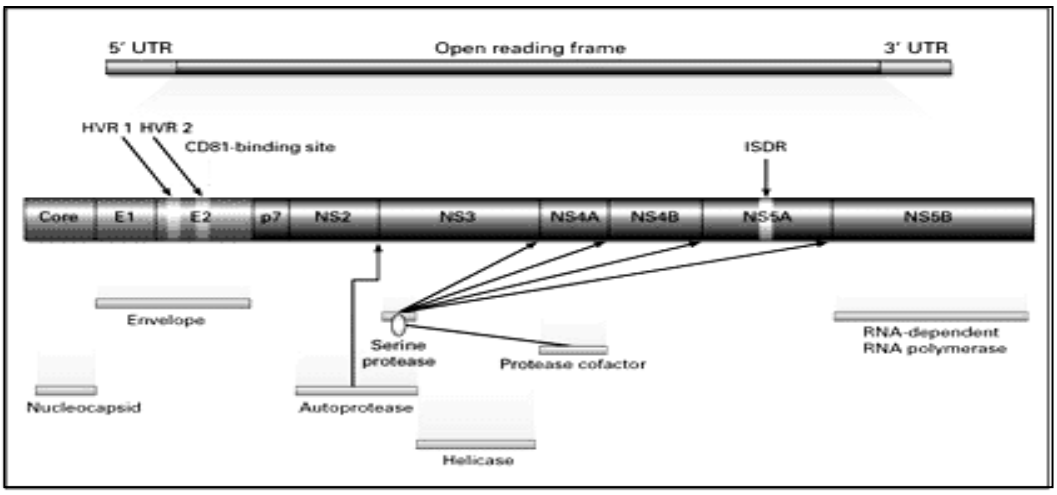

Figure (2): The HCV Genome and Expressed Polyprotein
(Houghton et al., 2009)

Structural components include the core and 2 envelope proteins, El and E2. Two regions of the E2 protein, designated hypervariable region 1 and 2, have an extremely high rate of mutation, thought to result from selective pressure by virus-specific antibodies ***(Houghton*, *2009)*.**

The nonstructural components include NS2, NS3, NS4A, NS4B, NS5A, NS5B, and p7, whose proteins function as helicase, protease, and RNA-dependent RNA polymerase, although the exact function of p7 is unknown. One region within NS5A is linked to an interferon (IFN) response and is called the IFN sensitivity-determining region. These enzymes

are critical in viral replication and are attractive targets for future antiviral therapy ***(Houghton, 2009).***

There are six main genotypes, each of which contains closely related subtypes. Molecular epidemiological studies have shown marked differences in the genotype distribution by geographical region and between patient groups. ***E1-Zayadi (2007)*** found that the predominant HCV genotype in Egypt is 4a which shows limited response to treatment. HCV genotype 1 may play a role in the development of HCC, and Taiwan is one of the countries having high incidence of hepatitis C virus (HCV)-related (HCC), although some studies have argued against this ***(E1-Zayadi et al.,2007)***.

It is well known that HCV genotypes 2 and 3 which are prevalent in North America, Europe, Japan, Taiwan and parts of China, Thailand, Singapore and other parts of Southeast, patients have significantly higher sustained response rates (SVR) to treatment compared to genotypes 1 and 4 patients. Prior studies have also demonstrated that 12-14 weeks treatment by pegylated interferon and ribavirin is effective in genotype 2 or 3 HCV patients who become HCV undetectable after 4 weeks of therapy rapid virologic response (RVR) or super responders (SR) ***(Simmonds et al., 2003).***

Risk groups for transmission of HCV:

1. Transfusion recipient:

Hepatitis C is a viral infection mainly parenterally transmitted, discovered in context of transfusion associated hepatitis in 1989. The introduction of blood screening programs has dramatically reduced infection in blood and blood products recipients. The risk of transmission of HCV via blood transfusion is minimal because of donor screening and testing and is associated with donation collected during window period ***(Talaat et al., 2003)***.

2. Sexual transmission (HIV Co-infection):

The HCV can be transmitted by sexual contact but much less efficiently than other sexually transmitted viruses, including hepatitis B virus and human immune deficiency virus (HIV). Risk of HCV transmission by sexual contact differs by the type of sexual relationship. Person in long-term monogamous (the practice of having only one wife or husband at one time) partnership are at lower risk of HCV acquisition than persons with multiple partners. In seroprevalence studies in monogamous, heterosexual partners of HCV-infected, HIV-negative persons, the frequency of antibody positive and genotype concordant couples is 2.8% to 11% in South East Asia, 0% to 6.3% in Northern Europe, and 2.7-10% in the United States. HIV-HCV co-infection magnified the risk of sexual transmission of HCV to both heterosexual and gay men. The finding suggest that HCV is being increasingly sexually transmitted particularly among HIV-positive ***(Magder et al., 2005).***

3. Drug Injection:

Injection drug users (IDUS) constitute the largest group of persons at high risk for acquiring hepatitis C virus infection in developed countries during the past two decades ***(Magder et al., 2005).***

The prevalent ranged from 50-95% among those groups. Studies have now shown that HCV transmission among IDUS is associated with both direct and indirect sharing of injection equipments such as cookers and cotton ***(Magder et al., 2005).***

4. Organ Transplantation:

Because a number of studies have associated infections with HCV with increased morbidity and mortality among renal transplant recipients, it is important to prevent HCV transmission with renal transplantation. Transplantation of organ from anti-HCV positive donors into anti-HCV positive recipients has been found to be safe. An even better alternative might be a policy of transplanting kidneys from anti-HCV positive donors only in HCV-RNA positive recipients. Donor screening remains the primary method of preventing transmission of viral infections from organs and tissues. However, this is not enough to prevent infection transmission ***(Magder et al., 2005)***.

The ***clearant process*** (Trade mark) offers great promise in preventing future cases of viral transmission, a patented process based on gamma irradiation, the ***clearant process*** (Trade mark)

substantially inactivates all types of known pathogens, including viruses, bacteria, fungi and priors, in the final package without damaging the structural integrity of the tissue ***(Magder et al., 2005)***.

5. Health care worker:

Doctors, nurses, and laboratory personnel have a higher prevalence of hepatitis C than the general population. Exposure to blood products from poor safety precautions or from accidental needle sticks seems to increase their risk of acquiring the disease ***(Marranconi et al., 2002).***

6. Hemophilic patients:

Rate of post-transfusion hepatitis in hemophilic patients was determined to be between 8% and 10%. Effective blood screening for the virus was developed and implemented by 1990, which lowered the rate of post-transfusion hepatitis to less than 5% from 1990-1993. Since then, improved testing has led to drastic reductions in risk, down to less than 1% after 1993. Incidence of hepatitis C infection among hemophiliacs remained high through, because plasma used to treat hemophilia is often a mixture from many different donors ***(Manzin et al., 2009).***

7. Patients on dialysis:

Hepatitis C can be transmitted through dialysis equipment that is not properly disposed of or disinfected. Prevalence of HCV infection among chronic patients on dialysis is 1.4%. HCV-related liver disease is mostly asymptomatic in patients on long-term dialysis ***(Mcelborough et al., 2001).***

Clinical Manifestation and Sequel of HCV Infection:

1. Acute hepatitis C:

The estimated incubation period is 7 weeks. Children and adults who acquire the infection usually are asymptomatic, or have a non-specific clinical illness characterized by fatigue, malaise, anorexia and weight loss ***(Ozaras and Tahan, 2009)***.

Only 25-30% of adults that acquire HCV infection may suffer from jaundice. Symptoms typically last for 2-12 weeks, during this period the ALT levels may be increased tenfold, with detection of HCV-RNA by polymerase chain reaction (PCR) ***(Ozaras and Tahan, 2009)***.

2. Chronic hepatitis and cirrhosis:

At least 85% of individuals acutely infected with HCV develop chronic HCV infection. Chronic infection with hepatitis C virus (HCV) is the leading cause of cirrhosis and the most common indication for liver transplantation in many countries throughout the world. The most significant factors leading to