Introduction

Hepatitis C is the most common cause of chronic viral liver disease in haemodialysis patients ***(Hinrichsen et al., 2002)*** Hemodialysis (HD) patients have an increased risk of exposure to hepatitis C virus (HCV). The relevance of HCV infection in HD patients is due to the documented increased risk of death due to chronic liver disease in these patients, particularly after kidney transplantation ***(Nemati et al., 2009).***

The natural course of hepatitis C in haemodialysis patients is not well understood. It seems to differ from that in other HCV patients ***(Simon et al., 1994).*** Liver function tests are close to or near normal in many case ***(Guh et al., 1995)*** but the mortality of HCV infected haemodialysis patients seems to be enhanced compared with HCV negative haemodialysis patients in preliminary studies ***(Stehman-Breen et al., 1998).*** Thus patients with HCV on chronic haemodialysis are at increased risk of death, which suggests that the focus should be directed more to identification and prevention of hepatitis C infection in haemodialysis patients.

The prevalence of HCV infection among HD patients varies from country to country and from one center to another. The reported prevalence of HCV infection among dialysis patients in developed countries ranges from 3.6 to 20%; ***(Jadoul et***

al., 2004). it is much higher in developing countries ***(Jaiswal et al., 2002).*** The prevalence of anti-HCV among dialysis patients was 0.4% in the 8.4% in the United States (2000) 43.9% in Saudi Arabia (2001), 30% in India (2002), and 41% in Turkey (2001) ***(Tokars et al., 2002).*** In Egypt according to the Egyptian renal registry the prevalence is 52.1 % ***(Afifi, 2009).***

Dissemination in HD centers. Repeated blood transfusions, shared dialysis machines, surgery, nosocomial route and multi-dose drug vials are the major suggested routes for spread of HCV infection in HD unit ***(Nobakht Haghighi et al., 2001).*** Partial immunosuppression found in HD patients, resulting in a poor antibody response, may play a role in sensitizing them to acquire the infection through uncommon ways.

The extensive use of recombinant erythropoietin to correct renal anemia in haemodialysis patients resulted in a significant reduction in blood transfusions. However, previous studies have shown that de novo infections in single haemodialysis units may still occur in the absence of other parenteral risk factors ***(Fabrizi et al., 1998)***.

In recent years, HCV viraemia (HCV-RNA) has been routinely detected by polymerase chain reaction (PCR) ***(Gretch et al., 1995).*** In 1993, Bukh and colleagues were the first to describe the fact that HCV viraemia can occur without detection of HCV

antibodies. This has been confirmed by several authors in small patient populations ***(Seeling et al., 1994).*** Most epidemiological studies in haemodialysis patients have been performed using serological testing of hepatitis C antibodies only ***(Fabrizi et al., 1993).*** Several prevalence studies of hepatitis C have been undertaken. There is a wide range in HCV antibody positivity and HCV viraemia within the studies, ranging from 1% up to 91%.

Aim of Work

The aim of this multicenter study is to retrospectively investigate the HCV seroconversion and prevalence of hepatitis C virus (HCV) infection among haemodialysis patients in Alexandria governorate (sector B) and delineate events and factors associated with HCV seroconversion collected from these centers

(Al Ameria City, Al-Gomrok district, Borg Al Arab City and Western district).

Hepatitis C Virus (HCV) Infection

The hepatitis C virus (HCV) is a major public health problem and a leading cause of chronic liver disease (***Williams, 2006).***

Hepatitis C is the principal cause of death from liver disease and the leading indication for liver transplantation in the U.S ***(Kim, 2002)***.

Epidemiology:

It is difficult to determine the number of new HCV infections, as most acute cases will not be noticed clinically. Fewer than 25% of acute cases of hepatitis C are clinically apparent. In addition, the age of infection upon diagnosis is not possible to determine in most cases. Nevertheless, it has to be assumed that the number of new infections has considerably decreased over the past decades ***(Wasmuth, 2009).***

For the United States it is estimated that the number of new cases of acute HCV infection has fallen from approximately 230,000 per year in the 1980s to about 20,000 cases per year currently. This decrease is primarily associated with reduced infections in injection drug users, a probable consequence of changes in injection practices motivated by education about human immunodeficiency virus (HIV) transmission ***(Wasmuth, 2009).***

Hepatitis C in Egypt

The World Health Organization has declared hepatitis C a global health problem, with approximately 3% of the world's population (roughly 170-200 million people) infected with HCV. In the US, approximately 3 million people are chronically infected, many of whom are still undiagnosed. In Egypt the situation is quite worse. Egypt has a population of 62 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 10-13% ***(Mohamed, 2004).***

Egypt has the largest epidemic of hepatitis C virus (HCV) in the world. The recently released Egyptian Demographic Health Survey (EDHS) tested a representative sample of the entire country for HCV antibody. The sample included both urban and rural populations and included all 27 governorates of Egypt. Over 11,000 individuals were tested.

The overall prevalence (percentage of people) positive for antibody to HCV was 14.7%.

14.7% the number of Egyptians positive for HCV antibody.

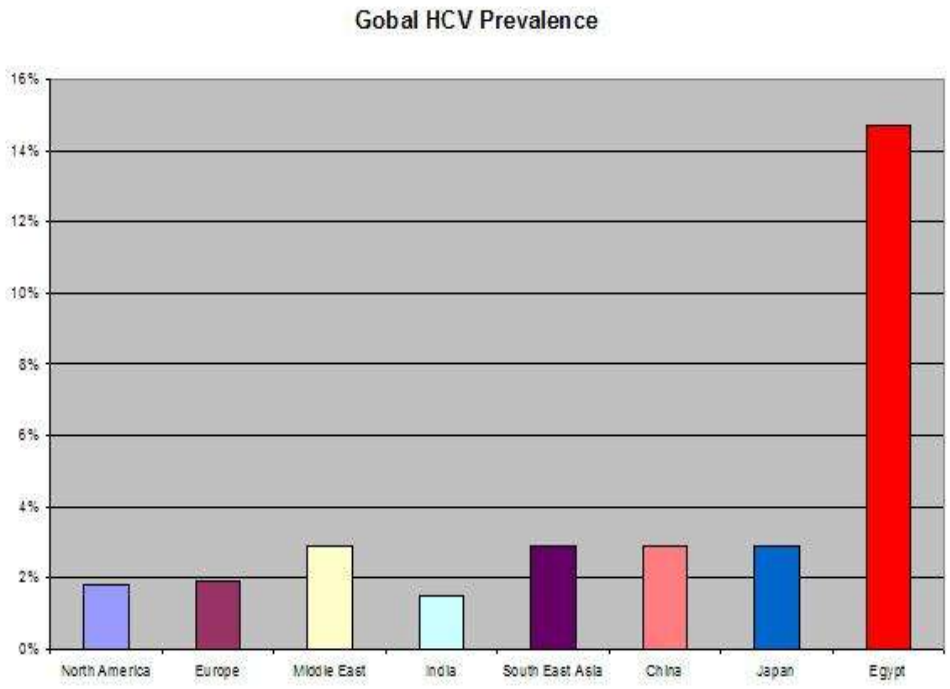

Figure (1): Hepatitis C virus in Egypt compared to other countries in the world (***El-Zanaty et al., 2009)***

Hepatitis C virus in Egypt compared to other countries in the world is shown in the next graph.

The current population in Egypt is about 78 to 80 million. 14.7% of this population (0.147 X 78 million) is 11,466,000 persons who have been infected with this virus. This number is an underestimate because it does not include the number of people who have been infected that are under 15 years of age or over 60 years of age. Not everyone remains infected but EDHS reported that 9.8% continue to have HCV RNA. That means almost 10% of the total population are infected and are infectious to other

people. That is 7.8 million people with chronic active HCV infection. This also is an underestimate because it does not include the number of people who have been infected that are under 15 years of age or over 60 years of age that are chronically infected (***El-Zanaty et al., 2009)***.

Interestingly, genotype 4 represents over 90% of cases in Egypt. Although subtype 4a is the dominant Egyptian HCV strain, a survey by ***(Ray et al., 2000)*** of HCV genetic diversity in the country revealed that other subtypes (provisionally named 4 , 4ß, and 1g) are also present at lower prevalences. The most recent common ancestor of each subtype (including 4a) existed approximately 80–120 years ago, suggesting the recent and simultaneous appearance of a few pre-existing endemic strains. This is in contrast to the pattern of HCV genetic diversity found in other developing regions, which is more consistent with a long period of endemic infection ***(Pybus et al., 2001)***.

Chronic HCV is the main cause of liver cirrhosis and liver cancer in Egypt and, indeed, one of the top five leading causes of death. In Egypt, the major route of exposure appears to be due to injection therapy and inadequate infection control practices. In addition to blood transfusions prior to 1994, the major risk factor associated with HCV infection is a history of antischistosomal injection treatment before 1986 ***(Mohamed, 2004)*** .

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. The PAT (parenteral antischistomal therapy) campaign would have been particularly effective at transmitting blood-borne pathogens for several reasons. First, the tartar emetic was given in 10 to 12 intravenous doses spaced by one week, allowing for the onset of infectious viremia (2-4 weeks for HCV) in patients still undergoing treatment. Furthermore, the injections were administered to mixed age groups, matching higher-prevalence groups to lower-prevalence ones (particularly children). The absence of symptoms in the majority of acute HBV and HCV infections, and the masking side effects of PAT, meant that the burgeoning epidemic went unnoticed and "thus, effective cycles of infection within the treatment units could have been established and sustained ***(Frank et al., 2000).***

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. Furthermore, the hypothesis is supported by high prevalence rates of anti-HBc

(indicating exposure to HBV), which is expected due to HBV's greater infectiousness ***(Arafa et al., 2005).***

Schistosomiasis used to be a common parasitic disease in Egypt acquired through swimming or wading in contaminated irrigation channels or standing water. Thus, farmers and rural populations were at greatest risk, and this is supported by the higher prevalence rate of HCV in the Nile delta and rural areas.

Schistosomiasis can lead to urinary tract or liver damage over many years. Prior to 1986 the mainstay of treatment was intravenous tartar emetic ***(Mohamed, 2004)***.

Further, with such a high background prevalence rate, transmission of hepatitis C other non medical routes has become more significant. For example, tattooing, circumcision or other medical procedures performed by non-medical personnel are more frequent routes of infection in Egypt than elsewhere. In addition, household transmission, vertical transmission and sexual transmission are routes that are also under investigation ***(Mohamed, 2004).***

As expected, the availability and cost of treatment for hepatitis C in Egypt is quite prohibitive. Although the most common methods of previous hepatitis C transmission (injection-based treatment for schistosomiasis and blood transfusions) have been addressed, the prevalence in those under age 20 is still

approximately 5-8%, demonstrating the continued presence of significant hepatitis C transmission in modern-day Egypt ***(Mohamed, 2004).***

A high level of infection with the hepatitis C virus (HCV) has long been recognized in rural Egypt. A substantial number of infected people in the population are not aware of their infective status and are not clinically ill, but are a source of infection for others. As yet, there is no vaccine against the virus, and current multi-drug treatment to eliminate the virus is inefficient, costly and has serious side-effects. Thus, the most effective control strategy is primary prevention so that people will not become infected in the first place ***(Poynard et al., 2003)***.

HCV structure:

HCV is a positive strand RNA virus of approximately 9.6 Kb in length. Its genome is composed of a 5'non-coding region (5'NCR), a long open reading frame (ORF) encoding a polyprotein precursor of about 3,000 amino acids and 3'NCR. The 5'NCR functions as internal ribosomal entry site (IRES) essential for cap independent translation of the viral RNA ***(Bartenschlage et al., 2004)***.

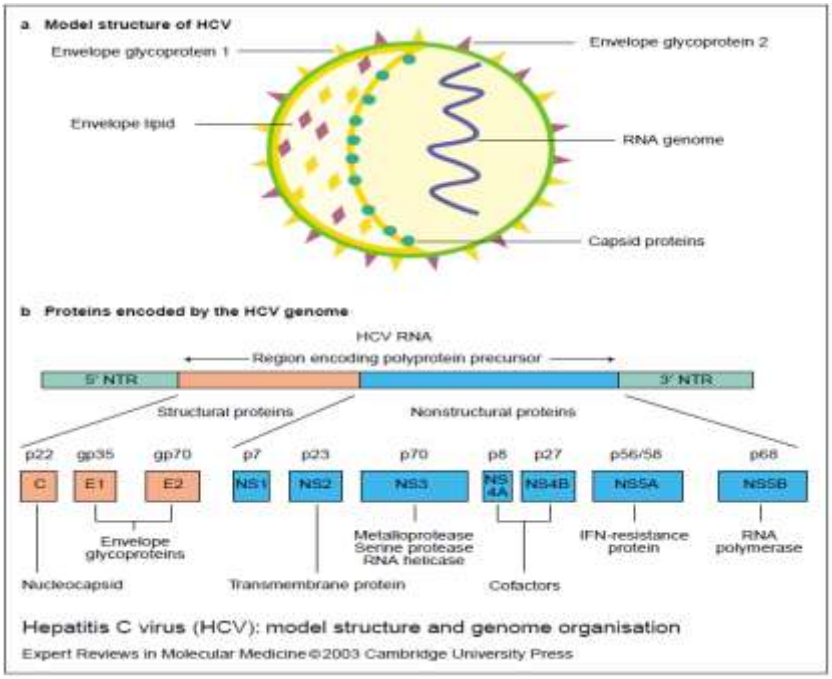

Figure (2): Hepatitis C virus (HCV): model structure and genome organisation.

(a) Model structure of HCV. The left-hand side of the illustration shows the viral surface of envelope lipids and glycoproteins; the right-hand side shows the RNA genome encased by capsid proteins. (b) Proteins encoded by the HCV genome. HCV is formed by an enveloped particle harbouring a plus-strand RNA of ~9.6 kb. The genome carries a long open-reading frame (ORF) encoding a polyprotein precursor of 3010 amino acids. Translation of the HCV ORF is directed via a ~340 nucleotide long 5' nontranslated region (NTR) functioning as an internal ribosome entry site; it permits the direct binding of ribosomes in close proximity to the start codon of the ORF. The HCV polyprotein is cleaved co- and post-translationally by cellular and viral proteases into ten different products, with the structural proteins [core (C), E1 and E2] located in the N-terminal third and the nonstructural (NS2-5) replicative proteins in the remainder. Putative functions of the cleavage products are shown.

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The core region has numerous functional activities. These include its role in encapsulation of viral RNA, a regulatory effect on cellular and viral promoters, interactions with a number of

cellular proteins, a modulator role in cell death under certain conditions, involvement in cell growth promotion and immortalization, induction of HCC in transgenic mice and a possible immuno-regulatory role ***(Ray and Ray, 2001)***.

HCV Genotypes:

HCV displays significant genetic heterogeneity as a result of accumulation of mutations during replication. The genetic heterogeneity is not uniform across the genome, the most highly conserved regions of the genome are parts of the 5'NCR and the terminal 3'NCR followed by the core region. In contrast, the most heterogeneous portions of the genome are the genes encoding the envelope proteins (E1 and E2). Accumulation of nucleotide substitution in the HCV genome results in diversification and evolution into different genotypes and subtypes. No fewer than 6 genotypes and more than 50 subtypes have been detected ***(Kato, 2001).***

Each of the six main genotypes of HCV is equally divergent from one another and varies by as much as 35% of nucleic acid content, while subtypes within a typical genotype differing from each other by 20-23%. Within the infected host the viral pool comprises several different but closely related sequences called quasispecies; these may show up to 10% diversity ***(Omran et al., 2009).***

Current classifications distinguish between 6 major genotypes and multiple subtypes, and very recently a novel seventh genotype has been described ***(Murphy et al., 2007)***.

These HCV genotypes differ in their genetic structure, clinical features, and their geographical distribution. Genotype 1b is observed worldwide, whereas genotypes 1a and 3a are regionally concentrated in European and North American countries, genotype 2 in the Mediterranean region, far east and Western Africa, genotype 5 in South Africa, genotype 6 in South East Asia ***(Simmonds et al., 2005)***, and genotype 7 was found in patients from the Democratic Republic of Congo ***(Murphy et al., 2007)***.

Genotype 4 is encountered throughout Africa and Mediterranean countries, but more recently has spread to Europe and North America mostly by immigrants and injection drug users significant frequencies of genotype 4 infections have also been reported in India and the Caribbean ***(Nguyen and Keeffe, 2005).***

There is increasing evidence that patients infected with different HCV genotypes have different clinical profiles, severity of liver disease and response to alpha-interferon therapy. Hence, a convenient and reliable HCV genotyping system is essential for large-scale epidemiological and clinical studies ***(Franciscus, 2007).***

Transmission:

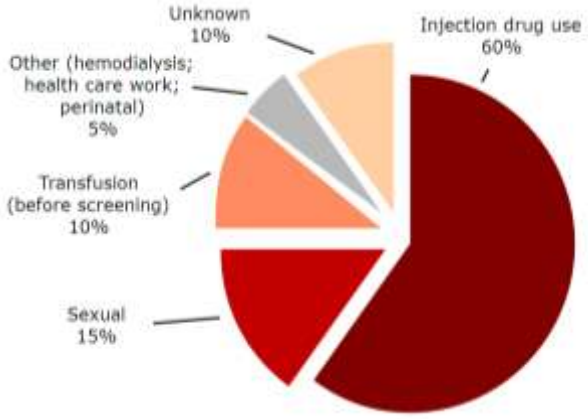

Figure (3): Hepatitis C infection in the US by source ***(CDC, 2001).***

Sexual activities and practices were initially identified as potential sources of exposure to the hepatitis C virus. More recent studies question this route of transmission ***(Tohme & Holmberg, 2010).***

Modes of transmission

1. **Injection drug use:**

Those who currently use or have used drug injection as their delivery route for drugs are at increased risk for getting hepatitis C because they may be sharing needles or other drug paraphernalia (includes cookers, cotton, spoons, water, etc.), which may be contaminated with HCV-infected blood. An estimated 60% to 80% of intravenous recreational drug users in the United States have been infected with HCV Harm reduction strategies are encouraged in many countries to reduce the spread of hepatitis C, through education, provision of clean needles and syringes, and safer injecting techniques ***(CDC, 2001).***