INTRODUCTION

Hepatitis C virus (*H*CV) is endemic in many countries and is a growing burden for society and health-care systems. The massive increases in long-term sequelae such as cirrhosis and hepatocellular carcinoma (HCC) are a particular problem ***(Grebely et al, 2011).***

The estimated number of chronically infected HCV patients worldwide is about 180 million ***(Messina et al., 2015).***

Egypt has the highest level HCV prevalence in the world, the percentage of adults (aging from 15-59 year) testing positive on the HCV RNA test is 7% of the Egyptian population (***Kandeel et al., 2017).***

Clinical care for patients with HCV-related liver disease has advanced considerably during the last two decades, due to an enhanced understanding of the pathophysiology of the disease, and because of developments in diagnostic procedures and improvements in therapy and prevention. ***(Alessio ,2014).***

Sofosbuvir (SOF) is a nonstructural 5B polymerase inhibitor with activity in all HCV genotypes and is the backbone of many anti-HCV drug regimens. SOF is initially converted into a pharmacologically active form in the liver and subsequently into an inactive metabolite that undergoes renal excretion. This poses a particular challenge for using SOF in HCV patients with renal impairment .SOF exposure is 450%

higher in patients with an estimate glomerular filtration rate eGFR) < 30 mL/minute/1.73 m^2. As a result, the use of SOF not recommended in GFR <30 (***Paula Cox-North et al., 2017)***.

A previous study showed that at the end of treatment with sofosbuvir-based regimens, the eGFR level was significantly decreased and the Serum creatinne level was significantly increased at 24 week post-treatment, non-cirrhotic patients showed improvements, whereas a persistent decrease in eGFR level and increases in Serum creatinne level was observed in cirrhotic patients. eGFR and Serum creatinne level were important indices for assessing renal function. ***(Jianhong Chen et al., 2017).***

Aim of the Work

Assessment of changes in renal indices during and after HCV treatment in chronic hepatitis C patients treated with sofosbuvir /daclatasvir, with or without ribavirin with normal baseline creatinine.

Chapter 1
HEPATITIS C VIRUS

Epidemiology

Hepatitis C is a disease with significant global impact, about 130-150 million people chronically infected with HCV, representing about 2-2.5% of the world's population. In some countries, e.g., Egypt, the prevalence is 10% ***(WHO, 2016).***

In USA the number of new HCV infections has decreased from 230,000 per year in the 1980s to about 30,500 cases in 2014 ***(CDC, 2016).***

It is difficult to determine the number of new HCV infections, because most acute cases are asymptomatic. Fewer than 25% of acute cases of HCV are clinically apparent ***(Vogel et al., 2009).***

HCV in Egypt

Egypt is the country with the highest HCV prevalence in the world; in 2008, the Egyptian Demographic Health Survey (EDHS), which was conducted on a large nationally representative sample, estimated the prevalence of HCV antibodies and HCV RNA, among the 15–59 year age group, to be 14.7 and 9.8% respectively. Based on the population census and the EDHS done in 2008, it was estimated that more than

6.8 million persons aged 15–59 years had HCV antibodies, of which more than 4.5 million individuals had active HCV infection ***(El-Zanaty and Way, 2009).***

In DHS (2017) the percentage of adults aging from 15-59 testing positive on the HCV RNA test is 7% of the Egyptian population ***(Kandeel et al., 2017).***

The origins of the HCV epidemic in Egypt are not clear but thought to be due to iatrogenic exposures. Iatrogenic exposures and failure in infection control could be seen on visits to health care facilities throughout the large Egyptian health care system ***(Miller et al., 2015)***.

Historically, it started by the parentral anti-schistosomal treatment campaigns underwent in the 1960s and 1970s in rural areas using improperly sterilized glass syringes (tartar emetic injections) ***(Esmat, 2013).***

More than 2 million injections were given annually to an average of 250,000 patients. Over the 18 years of treatment, 36 million injections were administered to >6 million people, almost all with unsterilized and shared syringes and needles. This represents the largest ever iatrogenic spread of blood-borne infection ***(Frank et al., 2000)***

This is the main reason of the high HCV prevalence rate in rural than in urban areas; 12% and 7% respectively ***(El-Zanaty and Way, 2009).***

A report in 1997 showed an association between HCV antibodies and a history of parenteral anti-schistosomiasis treatment and surgery ***(El-Sayed et al., 1997).***

In 2000, a report in the Lancet suggested that the epidemic was due in part to the previous wide spread rural campaigns of parenteral anti-schistosomiasis treatment ***(Frank et al., 2000).***

The Egyptian medical care system embraced this report as the cause of the epidemic. More importantly, Egypt's physicians expected that since these campaigns had ended more than three decades ago, therefore transmission had ended as well ***(Miller et al., 2015)***.

If this was true, then epidemiologically the prevalence of HCV antibodies in Egyptians whom are 30 years old or younger should be similar to other countries. That is from 1% to 3% or less, HCV antibodies prevalence increase from the earliest age. There is now an evidence that there is an ongoing HCV epidemic in Egypt ***(Miller et al., 2015)***.

Transmission of HCV from person to person in Egypt is of course continuing, there are many ways this exposure can occur, the most common exposure to HCV infection in Egypt is from formal and informal medical and dental care. For example, injections of all kinds, blood tests or when blood is taken by syringe or by a lancet ***(Mohamoud et al., 2013)***.

There are many procedures and treatments that are percutaneous or cause bleeding, if the persons doing such procedures using non sterile equipment or materials or has not changed their latex gloves, they could be exposed to HCV infection ***(Mohamoud et al., 2013)***.

In 2006 a survey was conducted on large and small health care facilities showed a defect in infection control practices in all facilities. In that study the presence or absence of infection control programs was an index of iatrogenic exposure to HCV ***(Talaat et al., 2006).***

HCV prevention in Egypt is a national priority. Policymakers and public health and medical care stakeholders need to implement further prevention measures against the transmission routes of infection. Scientific research needs to be expanded to measure current HCV incidence rate and to identify HCV modes of transmission in medical care, community, and household settings.

Such studies will develop effective prevention interventions. It is also essential to develop cost-effective strategies for treatment and management of the large pool of chronic HCV patients in Egypt ***(Mohamoud et al., 2013).***

The causative agent and virology

Taxonomy

HCV is a small-enveloped virus with one single-stranded positive-sense RNA molecule of approximately 9.6 kb; it belongs to the genus hepacivirus, one of the Flaviviridae family ***(Ashfaq et al., 2011).***

The Flaviviridae family is divided into three genera: flavivirus, pestivirus, and hepacivirus. Flaviviruses as yellow fever virus, dengue fever virus and Japanese encephalitis virus. Pestiviruses as bovine viral diarrhea virus and classical swine fever virus. HCV, with about 6 genotypes and numerous subtypes, is a member of the hepacivirus genus ***(Leyssen et al., 2000; Smith et al., 2014).***

Structure:

HCV is a spherical, enveloped RNA virus, with 50nm diameter; which consists of a positive RNA strand surrounded by a nucleocapsid, which is surrounded by two envelope proteins ***(Lauer and Walker, 2001).***

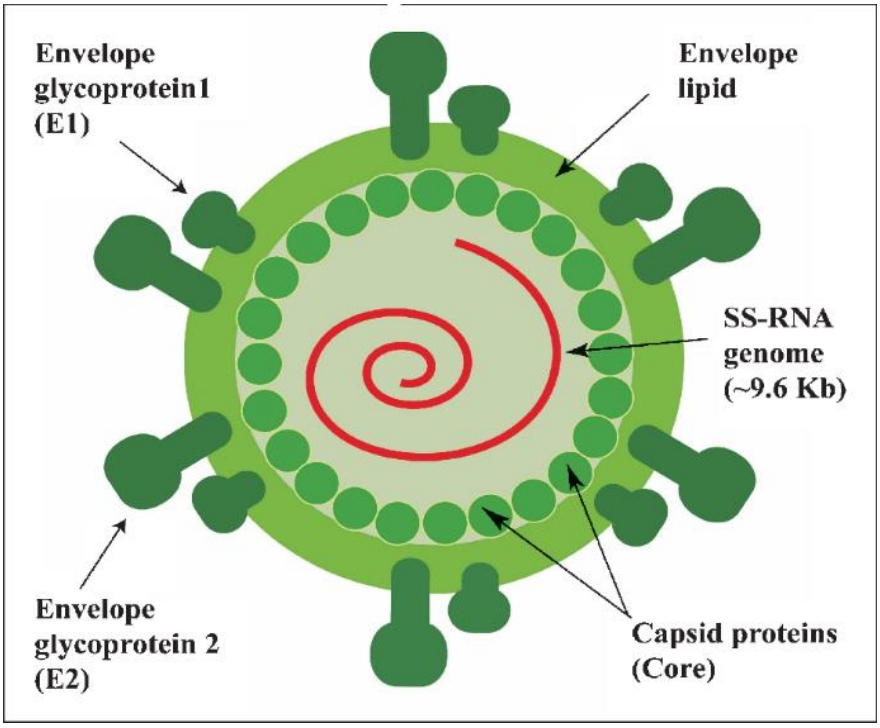

Figure (1): Hepatitis C virus particle structure ***(Wakita et al., 2005).***

The Genome:

The genome of HCV consists of one 9.6 kb single-stranded RNA molecule positive in polarity. The genomic RNA of hepatitis C virus serves as messenger RNA (mRNA) same as the other positive-strand RNA viruses, for the translation of viral proteins ***(Kupfer et al., 2009).***

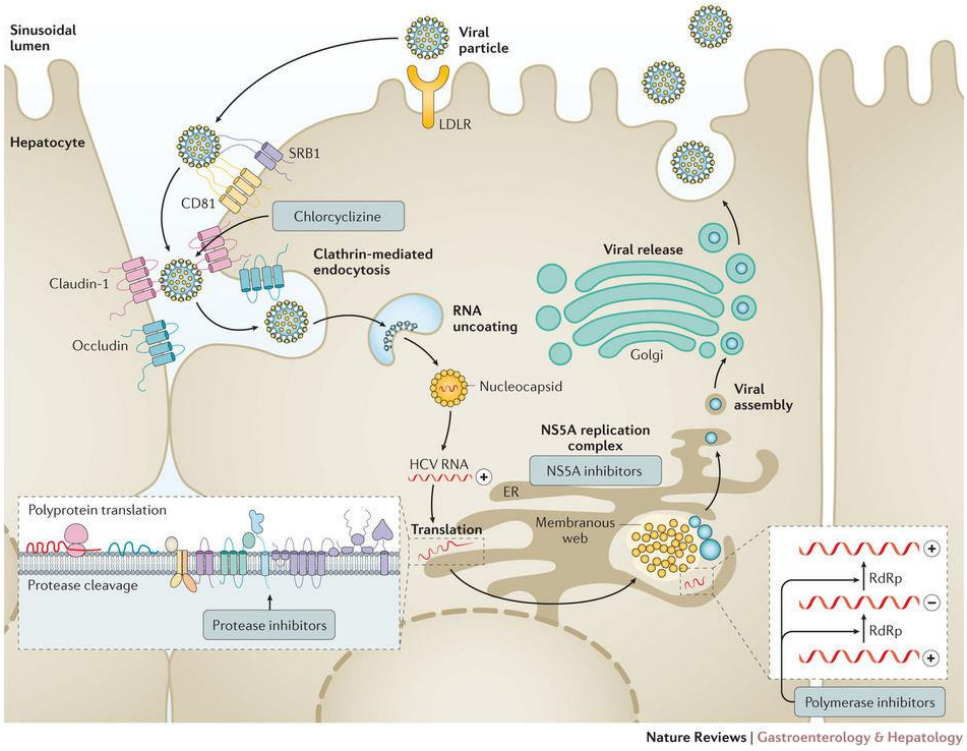

Figure (2): HCV life cycle and site of action of DAAs ***(Götte and Feld 2016).***

The linear molecule contains a single open reading frame (ORF) coding for a precursor polyprotein of about 3000 amino acid residues. The polyprotein is cleaved during viral replication by viral as well as host enzymes into 3 structural proteins (core, E1, E2) and 7 nonstructural proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). An additional protein termed F (frameshift) or ARF (alternate reading frame) has been predicted as a result of ribosomal frameshifting during translation within the core-region of the genomic RNA ***(Branch et al., 2005).***

At the 5' terminus of the open reading frame the structural genes encoding the viral core protein and the viral envelope proteins E1 and E2 are located followed downstream by the coding regions for the non-structural proteins p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B (Figure: 3).

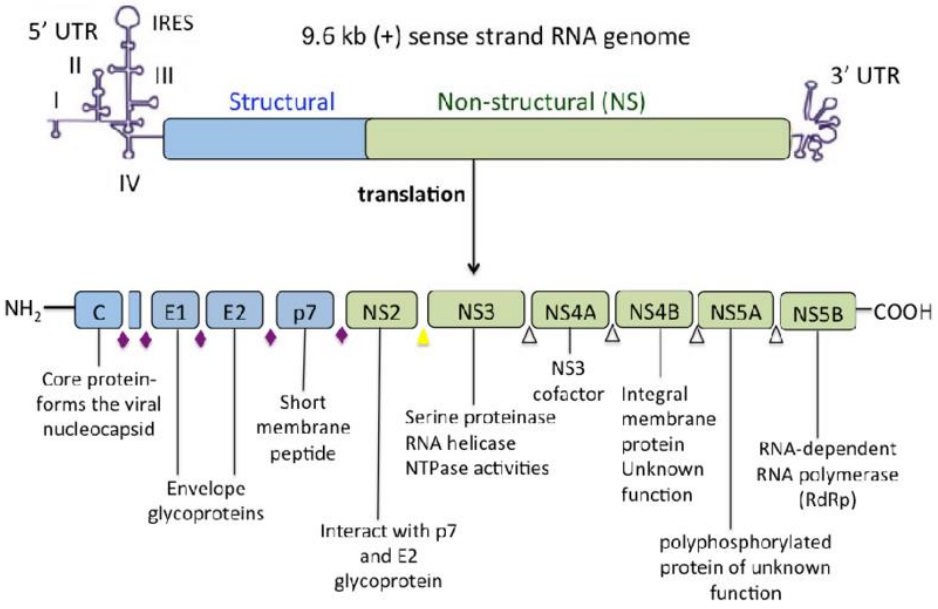

Figure (3): HCV genome organization and translation ***(Baharuddin et al., 2014).***

The structural proteins are essential components of the HCV virions, whereas the non-structural proteins are involved in RNA replication and virion morphogenesis ***(Kupfer et al., 2009).***

The ORF is flanked by 5' and 3' non-translated regions (NTR) which can also termed untranslated regions (UTR) or noncoding regions (NCR) containing nucleotide sequences relevant for the regulation of viral replication. Other NTRs

harbor highly conserved regions in comparison with the protein encoding regions of the HCV genome. The high grade of conservation of the NTRs makes them candidates for improved molecular diagnostics, as targets for antiviral therapies and as targets for anti- HCV vaccines ***(Kupfer et al., 2009).***

Variants and Heterogencity:

Due to the lack in virus proof-reading mechanisms HCV has a high rate of replication and turnover. The viral RNA polymerase introduces random nucleotide errors during replication, those errors can't be corrected, so the spontaneous nucleotide substitution rate of the virus is very high. This result in amino acid changes, that alter the biology of the virus and the virus as a whole is continually undergoing genetic evulsions and developing mutations. That is why HCV is a very heterogeneous virus ***(Elena and Sanjuán 2005).***

The heterogencity is maximum at the 5' terminus region of envelop protein (E2) and called hyper variable region (HVRI) which responsible for 60% of amino acid substitution. HCV heterogencity tend to generation of many different variants and epitopes which may have up to 34% difference in their nucleotide sequence ***(Tibbs and Smith, 2001).***

Frequent variation and new mutation make the virus able to escape the immune system, constantly to evade immune

detection, which lead to chronic infection in most cases, resistant to anti-viral therapy and a difficulty in development of a broadly reactive anti-HCV vaccine ***(Stoll-Keller et al., 2009).***

Quasispecies:

Heterogencity of the virus, lead to develop closely related groups of viruses with variants of genetic sequence (up to 1.5 %) which are thought to have evolved from a single dominant sequence within individual patients. So, HCV exists as a heterogeneous population of related viruses and that is what we call quasispecies, a high degree of quasispecies variability correlates with resistance of anti-viral therapy ***(Echeverría et al., 2015).***

Genotypes and subtypes:

Comparison of subgenomic regions such as E1, NS4 and NS5 have allowed us to classify variants into at least 6 main genotypes and over 50 subtypes. To be classified as separate genotype, the nucleotide sequence of an isolate will differ from others by 10% variations of 5% is used to define subtype ***(Tibbs and Smith, 2001).***

HCV genotypes classification are important from an epidemiological point of view due to the geographical distribution of some genotypes, for example genotypes 1, 2 and 3 are found in developed western countries, Japan and Australia

in various proportions, genotype 4 in middle east, genotype 5 in southern Africa and genotype 6 in Hong Cong and South-east Asia ***(Lauer and Walker, 2001).*** In Egypt, genotype 4 is the predominant genotype and subtype 4a represents over 90% of cases, most of other cases are genotype 1 ***(Stuart et al., 2000).***

HCV genotype also seems to affect the behavior of the virus regarding the response to anti-viral therapy, those patients infected with HCV genotypes 2 or 3 have better response to interferon-based therapies than those with HCV genotype1 ***(Pawlotskey, 2002).***

Genotyping may also predict the mode of transmission as genotype 1a and 3 are commonly found in injection drug users ***(Zein ,2000),*** the variability of HCV has a major implication for the development of new vaccines strategies; since there is no cross protection between different HCV types ***(Stoll-Keller et al., 2009).***

A study revealed the presence of at least 7 different HCV genotypes and 67 subtypes, however, the fast growing number of full-length HCV genome sequences may lead to higher numbers of HCV genotypes ***(Smith et al., 2014).***

Transmission

The most common risk factor of HCV is injection drug addiction, also patients undergoing hemodialysis and persons who are receiving blood transfusions regularly ***(Razavi et al., 2014).***

Modes of transmission:

■ **Blood-borne transmission is the predominant mode:**

- Injection drug use accounts for 85% of new cases in the United States.
- Transfusion of blood and blood products (now exceedingly rare in the United States and other developed countries, with an estimated risk of <1 per 2,000,000 units transfused)
- Hemodialysis
- Tattoos; body piercing
- Needlestick injury with a contaminated hollow-bore needle or blood splash to the eyes in a health care setting
- Cocaine snorting

■ Sexual transmission: Low efficiency, low frequency. Sexual transmission in men who have sex with men is recognized increasingly as a risk factor.

■ Maternal-neonatal transmission: Low efficiency, low frequency. The efficiency of transmission is increased with HIV coinfection. Transplacental passage of