INTRODUCTION

Metabolic syndrome is a set of risk factors that includes: abdominal obesity, a decreased ability to process glucose (increased blood glucose and / or insulin resistance), dyslipidemia, and hypertension. Patients who have this syndrome have been shown to be at an increased risk of developing cardiovascular disease and/or type 2diabetes. Metabolic syndrome is a common condition that goes by many names (dysmetabolic syndrome, syndrome X, insulin resistance syndrome, obesity syndrome, and Reaven's syndrome**)** ***(Rafiq et al., 2009).***

Metabolic syndrome is interrelated with conditions including cardiovascular disease, HIV disease, and liver disease, including chronic hepatitis C. Among hepatitis C patients, obesity and diabetes have been linked to both accelerated fibrosis progression and poorer response to interferon-based therapy**.**

Chronic infection with the hepatitis C virus (HCV) affects an estimated 170 million worldwide. Liver disease in those infected as adults may progress to cirrhosis and its complications in up to 25% over 25–30 years, contributing to significant morbidity and mortality. Disease progression is much slower when infection is acquired in childhood ***(Huang et al., 2007).***

Epidemiological data clearly indicate a link between chronic hepatitis C (CHC) and disturbed glucose homeostasis. The prevalence of both insulin resistance (IR) and type 2 diabetes mellitus (T2DM) is significantly higher in patients with CHC when compared with other chronic liver diseases. Consequently, it has become increasingly apparent that IR with or without concomitant T2DM influences long-term outcomes in CHC. Both reduce responsiveness to antiviral therapy and promote more rapid progression of liver disease to cirrhosis and hepatocellular carcinoma (HCC) ***(Elgouhari et al., 2009).***

The association between diabetes and CHC was first reported by significantly more prevalent in those with hepatitis C-related cirrhosis than those with cirrhosis resulting from conditions other than CHC (50 vs 9%). Since then, a number of studies have re-affirmed this association. The reported prevalence of T2DM in CHC ranges from 7.6 to 50%; confounding factors known to influence IR such as age, body mass index (BMI), viral load, viral genotype, advanced fibrosis and steatosis likely influence the variation in the prevalence reported ***(Kita et al., 2007).***

It is reported that 69.5% of individuals with CHC and Metabolic Syndrome have impaired glucose homeostasis. It therefore remains to be determined whether altered glucose metabolism (IR or T2DM) independently impairs the response to antiviral therapy and increases fibrosis *per se*, or whether this occurs in the context of inflammatory cytokines present in the obese state and metabolic syndrome, which may co-exist with and promote IR and T2DM ***(Cua et al., 2007).***

AIM OF THE WORK

To assess the role of metabolic syndrome in the response of treatment of hepatitis C with antiviral therapy.

Chapter （1）
HEPATITIS C VIRUS

Hepatitis C virus (HCV) is a small (55–65 nm in size) enveloped, positive-sense single-stranded RNA virus of the family Flaviviridae. Hepatitis C virus is the cause of hepatitis C in humans ***(Kapoor et al., 2011)***.

Taxonomy:

The hepatitis C virus belongs to the genus Hepacivirus a member of the family Flaviviridae. Until recently it was considered to be the only member of this genus. However a member of this genus has been discovered in dogs - canine hepacivirus.There is also at least one virus in this genus that infects horses ***(Burbelo et al., 2012)***.

Structure:

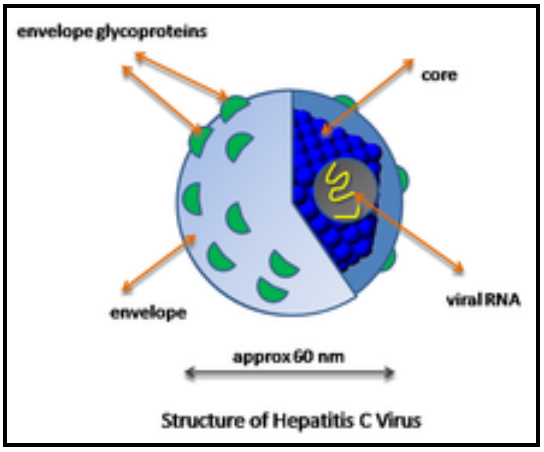

Fig. (1): Simplified diagram of the structure of the Hepatitis C virus particle ***(Adapted from Op De Beeck et al., 2003).***

The hepatitis C virus particle consists of a core of genetic material (RNA), surrounded by an icosahedral protective shell of protein, and further encased in a lipid (fatty) envelope of cellular origin. Two viral envelope glycoproteins, E1 and E2, are embedded in the lipid envelope (Figure 1) ***(Op De Beeck et al., 2003)***.

Genome:

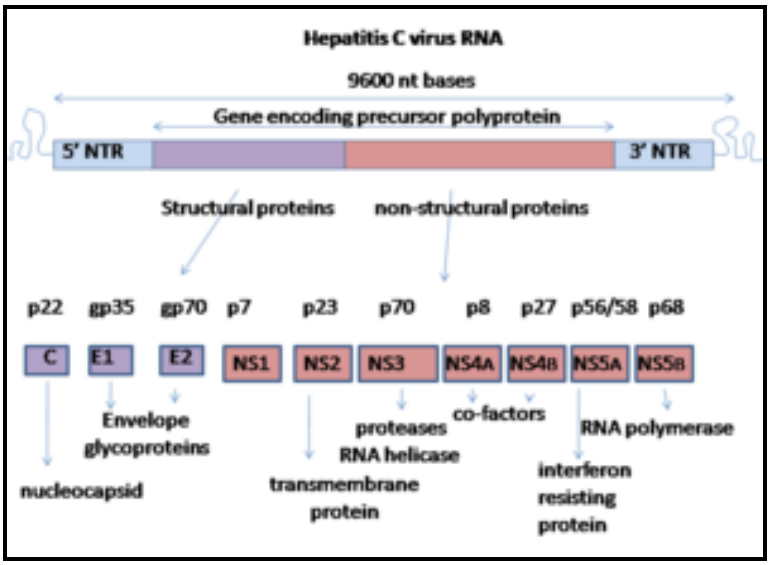

Fig. (2): Genome organisation of Hepatitis C virus ***(Adapted from Berry et al., 2011).***

Hepatitis C virus has a positive sense single - stranded RNA genome. The genome consists of a single open reading frame that is 9600 nucleotide bases long. This single open reading frame is translated to produce a single protein product, which is then further processed to produce smaller active proteins ***(Berry et al., 2011).***

At the 5' and 3' ends of the RNA are the untranslated region (UTR), that are not translated into proteins but are important to translation and replication of the viral RNA. The 5' UTR has a ribosome binding site (IRES — Internal ribosome entry site) that starts the translation of a very long protein containing about 3, 000 amino acids. The core domain of the hepatitis C virus (HCV) IRES contains a four-way helical junction that is integrated within a predicted pseudo knot. The conformation of this core domain constrains the open reading frame's orientation for positioning on the 40S ribosomal subunit. The large pre-protein is later cut by cellular and viral proteases into the 10 smaller proteins that allow viral replication within the host cell, or assemble into the mature viral particles.

Structural proteins made by the hepatitis C virus include Core protein, E1 and E2; nonstructural proteins include NS2, NS3, NS4, NS4A, NS4B, NS5, NS5A, and NS5B (Figure 2) ***(Berry et al., 2011).***

What is the nature (biology) of the hepatitis C virus?

'Hepatitis' means inflammation of the liver. HCV is one of several viruses that can cause hepatitis. It is unrelated to the other common hepatitis viruses (for example, hepatitis A or hepatitis B). HCV is a member of the Flaviviridae family of viruses. Other members of this family of viruses include those that cause yellow fever and dengue ***(Mohamed et al., 2000)***.

Viruses belonging to this family all have ribonucleic acid (RNA) as their genetic material. All hepatitis C viruses are made up of an outer coat (envelope) and contain enzymes and proteins that allow the virus to reproduce within the cells of the body, in particular, the cells of the liver. Although this basic structure is common to all hepatitis C viruses, there are at least six distinctly different strains of the virus which have different genetic profiles (genotypes). In the United state., genotype 1 is the most common form of HCV. Even within a single genotype there may be some variations (genotype 1a and 1b, for example). Genotyping is important to guide treatment because some viral genotypes respond better to therapy than others. The genetic diversity of HCV is one reason that it has been difficult to develop an effective vaccine since the vaccine must protect against all genotypes ***(Mohamed et al., 2000)***.

Replication:

Replication of HCV involves several steps. The virus replicates mainly in the hepatocytes of the liver, where it is estimated that daily each infected cell produces approximately fifty virions (virus particles) with a calculated total of one trillion virions generated. The virus may also replicate in peripheral blood mononuclear cells, potentially accounting for the high levels of immunological disorders found in chronically infected HCV patients. HCV has a wide variety of genotypes and mutates rapidly due to a high error rate on the part of the virus' RNA-dependent RNA polymerase. The mutation rate

produces so many variants of the virus it is considered a quasispecies rather than a conventional virus species. The virus enters into host cells occur through complex interactions between virions and cell-surface molecules CD81, LDL receptor, SR-BI, DC-SIGN, Claudin-1, and Occludin ***(Kohaar et al., 2010).***

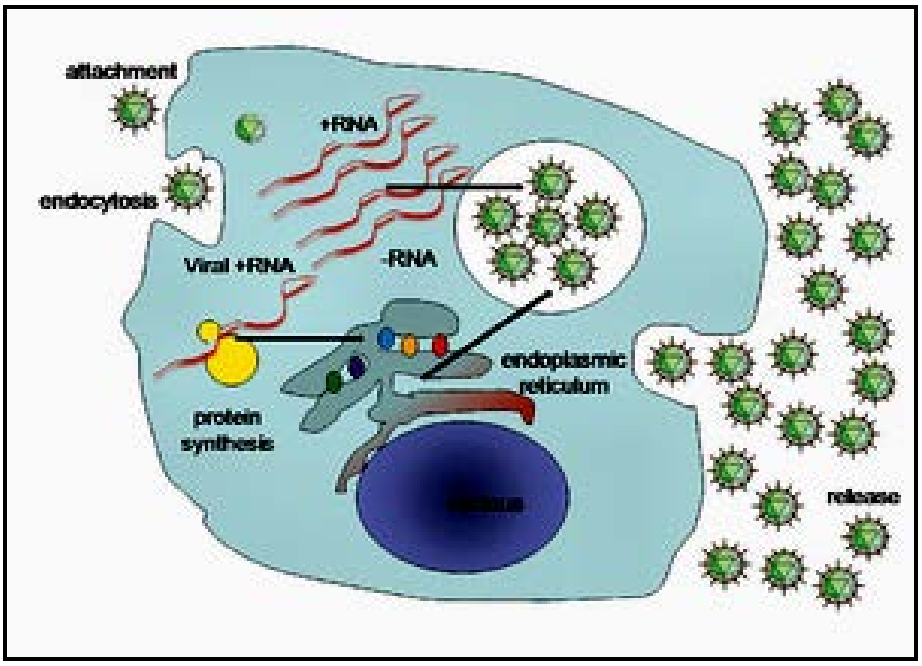

Fig. (3): A simplified diagram of the HCV replication cycle
(Adapted from, Syed et al., 2010)

Once inside the hepatocyte, HCV takes over portions of the intracellular machinery to replicate. The HCV genome is translated to produce a single protein of around 3011 amino acids. The polyprotein is then proteolytically processed by viral and cellular proteases to produce three structural (virion-associated) and seven nonstructural (NS) proteins.

Alternatively, a frameshift may occur in the Core region to produce an Alternate Reading Frame Protein (ARFP). HCV encodes two proteases, the NS2 cysteine autoprotease and the NS3-4A serine protease. The NS proteins then recruit the viral genome into an RNA replication complex, which is associated with rearranged cytoplasmic membranes. RNA replication takes places via the viral RNA-dependent RNA polymerase NS5B, which produces a negative strand RNA intermediate. The negative strand RNA then serves as a template for the production of new positive strand viral genomes. Nascent genomes can then be translated, further replicated or packaged within new virus particles. New virus particles are thought to bud into the secretory pathway and are released at the cell surface.

The virus replicates on intracellular lipid membranes. The endoplasmic reticulum in particular are deformed into uniquely shaped membrane structures termed 'membranous webs'. These structures can be induced by sole expression of the viral protein NS4B. The core protein associates with lipid droplets and utilises microtubules and dyneins to alter their location to a perinuclear distribution. Release from the hepatocyte may involve the very low density lipoprotein secretory pathway (Figure 3) ***(Syed et al., 2010).***

Genotypes:

Based on genetic differences between HCV isolates, the hepatitis C virus species is classified into seven genotypes (1-7) with several subtypes within each genotype (represented by lower-cased letters). Subtypes are further broken down into quasispecies based on their genetic diversity. Genotypes differ by 30-35% of the nucleotide sites over the complete genome. The difference in genomic composition of subtypes of a genotype is usually 20-25%. Subtypes 1a and 1b are found worldwide and cause 60% of all cases ***(Nakano et al., 2011).***

Hepatitis C virus genotype 4 (HCV-4) is the most common variant of the hepatitis C virus (HCV) in the Middle East and Africa, particularly Egypt. This region has the highest prevelance of HCV worldwide, with more than 90% of infections due to genotype 4. HCV-4 has spread in several Western countries, particularly in Europe, due to variations in population structure, immigration, and routes of transmission ***(Kamal, 1992).***

Clinical importance:

Genotype is clinically important in determining potential response to interferon-based therapy and the required duration of such therapy. Genotypes 1 and 4 are less responsive to interferon-based treatment than are the other genotypes (2, 3, 5 and 6). Duration of standard interferon-based therapy for

genotypes 1 and 4 is 48 weeks, whereas treatment for genotypes 2 and 3 is completed in 24 weeks. Sustained viral responses occur in 70% of genotype 1 cases, ~90% of genotypes 2 and 3, ~65% of genotype 4 and ~80% of genotype 6. Infection with one genotype does not confer immunity against others, and concurrent infection with two strains is possible. In most of these cases, one of the strains removes the other from the host in a short time. This finding opens the door to replace strains non-responsive to medication with others easier to treat ***(Yu et al., 2009).***

Epidemiology

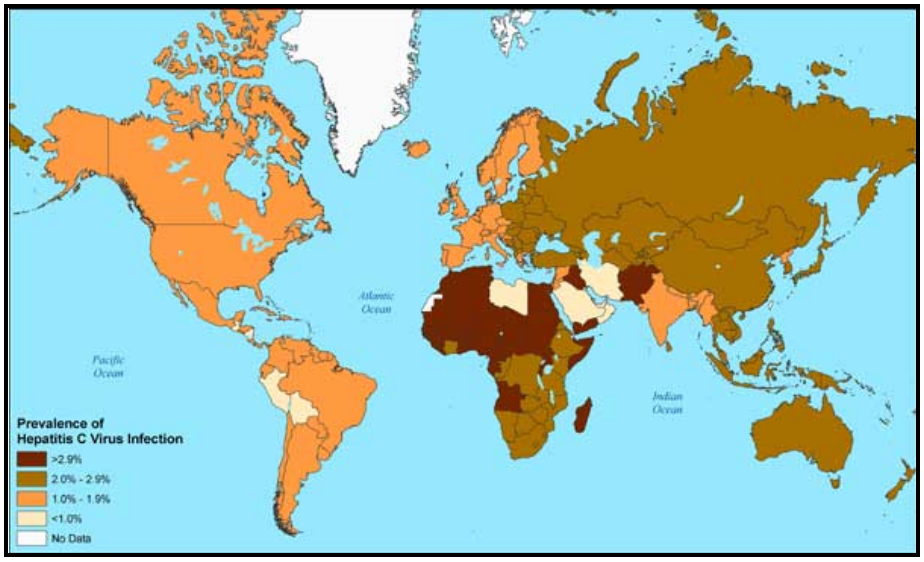

Fig. (4): Prevalence of hepatitis C worldwide in 2010
(Adapted from Muhlberger et al., 2009)

It is estimated that 130–170 million people, or ~3% of the world's population, are living with chronic hepatitisc

(Figure 4). About 3–4 million people are infected per year, and more than 350, 000 people die yearly from hepatitis C-related diseases.Rates have increased substantially in the 20th century due to a combination of intravenous drug use **(**IUD**)** and intravenous medication or poorly sterilized medical equipment. Among those chronically infected the risk of cirrhosis after 20 years varies between studies but has been estimated at ~10%-15% for men and ~1-5% for women. The reason for this difference is not known. Once cirrhosis is established, the rate of developing hepatocellular carcinoma is ~1%-4% per year ***(Mohamed et al., 2000).***

In the United States, about 2% of people have hepatitis C, with about 35, 000 to 185, 000 new cases a year. Rates have decreased in the Western world since the 1990s due to improved screening of blood before transfusion.Annual deaths from HCV in the United States range from 8, 000 to 10, 000; expectations are that this mortality rate will increase, as those infected by transfusion before HCV testing become apparent. Prevalence is higher in some countries in Africa and Asia. Countries with particularly high rates of infection include Egypt (22%), Pakistan (4.8%) and China (3.2%) ***(Saleh et al., 2008).***

Hepatitis C in Egypt

HCV epidemic in Egypt:

Egypt has the largest epidemic of hepatitis C in the world. The hepatitis C virus (HCV) epidemic in Egypt is unique in the world and well documented in the international medical scientific literature. The percentage of Egyptians with HCV is 14.7%. This is ten times greater than any other country in the world. The prevalence of HCV in Western countries is less than 2% **(Figure 5)**. The prevalence of HCV varies throughout the country. The northern Nile Delta appears to have the highest prevalence, ~28%. The much smaller population of Upper Egypt, in the south, seems to have the lowest HCV prevalence, ~ 16% ***(Saleh et al., 2008)***.

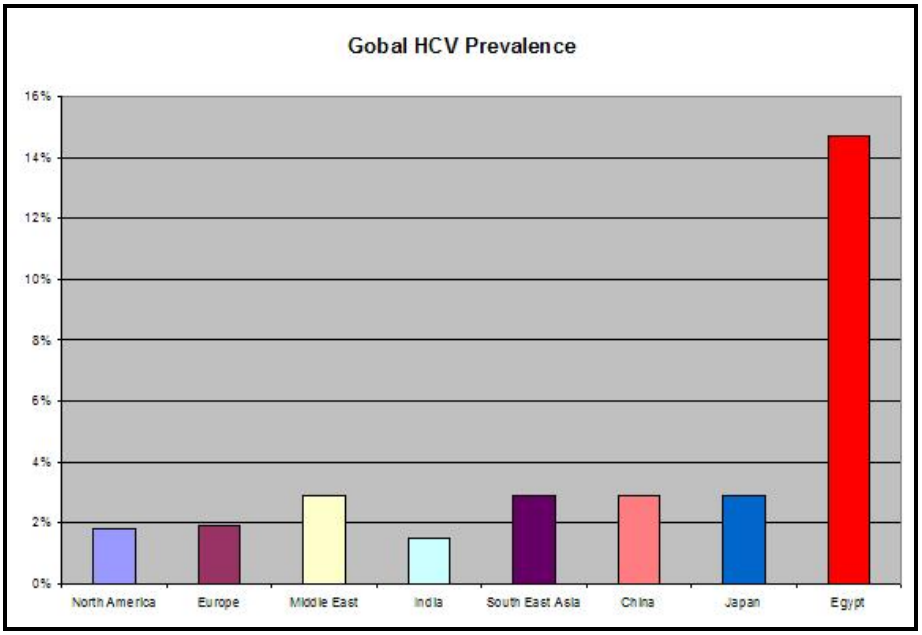

Fig. (5): Global HCV prevalence ***(Adapted from Christina et al., 2000).***

How the epidemic in Egypt was discovered?

The epidemic was first reported in the international medical literature in the journal Lancet, by Kamel et al. in 1992. This was the first year that a laboratory test (serologic assay) for HCV became globally available. Before this study no one really knew what the situation was in Egypt. Reports had been coming in from many countries, all in the 1% to 3% range. Egypt has a very large blood donation and transfusion system. The investigators designed a study based on first time blood donors. The report was based on the analysis of blood specimens from 2, 164 apparently healthy first time donors. 10.6% tested positive. This discovery had huge implications, the first was the issue of the blood supply and its safety. The HCV test was new and there were no policies in place to mandate HCV testing of blood donation. The Lancet report and other reports that soon followed, of course, changed altogether how the Egyptian system of blood banks were operated throughout the country ***(Kamel et al., 1992)***.

The study continued and in all collected and examined over 17,000 specimens. The additional specimens did not change the overall prevalence. The investigator's interpretation was that the prevalence was an underestimate for the general population. This is because the blood donors were apparently healthy first time donors. However, later published data provided a very clear pattern of prevalence and age ***(Christina et al., 2000)***.

Epidemiology of HCV infection in Egypt:

The hepatitis C epidemic in Egypt began during 1960–1980, when mass campaigns were conducted to control schistosomiasis through parenteral antischistosomal therapy (PAT) administered by health-care workers using improperly sterilized glass syringes. HCV transmission is ongoing in Egypt, and incidence rates have been estimated at 2.4 per 1, 000 person-years (165, 000 new infections annually). In 2008, nearly 15% of the population aged 15–59 years had antibodies to HCV (anti-HCV), and 10% (approximately 5 million persons) had chronic HCV infection; overall, an estimated 6 million Egyptians had chronic HCV infection in 2008. Prevalence of chronic HCV infection in Egypt is higher among men than women (12% and 8%, respectively), increases with age (reaching >25% among persons aged >50 years), and is higher among persons residing in rural versus urban areas (12% versus 7%) Primary modes of HCV transmission include unsafe injections, other inadequate infection control practices, and unsafe blood transfusions. HCV transmission also occurs among injection-drug users in Egypt ***(Paez et al., 2009)***.

Prevention:

No vaccine protects against contracting hepatitis C. However, a number are under development and some have shown encouraging results. A combination of harm reduction strategies, such as the provision of new needles and syringes