Review/ Epidemiology and natural history of Chronic Hepatitis C Virus infection

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ABSTRACT

It is believed that between 130 and 170 million individuals throughout the globe are infected with HCV. China has the highest number of people living with HCV of any nation in the world, with over 1% of the population afflicted (29.8 million). The burden of advanced liver disease varies greatly from country to country as a direct consequence of the disparities in HCV incidence in the past and HCV prevalence in the present, as well as the relatively gradual progression of HCV sickness. Over the next two decades, the prevalence of HCV-related cirrhosis and hepatocellular carcinoma (HCC) in nations with a high prevalence of HCV or a recent incidence peak would continue to rise. Acute HCV infection is hard to identify since the illness is often symptomless and at-risk groups are often marginalised. Approximately 25% of individuals with acute HCV infection clear the virus spontaneously, with higher rates among those with favourable IL28B genotypes, acute symptoms, and women. Chronic HCV infection, which increases the risk of hepatic fibrosis, cirrhosis, and HCC, affects the remaining 75% of patients. Although chronic hepatitis C tends to proceed slowly in its first two decades, ageing and co-factors like high alcohol consumption and HIV co-infection might speed up the disease during this time.

Keywords: HCV, chronic, epidemiology, cirrhosis

1- Introduction :

Hepatitis is characterised by inflammation of the liver and the existence of inflammatory cells in the organ's tissue; this inflammation may be self-limiting or lead to fibrosis and cirrhosis. Hepatitis can cause either no symptoms or a wide variety of uncomfortable ones, including jaundice, loss of appetite, and general malaise. It may be resulted from two; viruses that include those in "the hepatitis A, B, C, D, and E families", and non-viruses, including; "alcohol, certain medications, some organic solvents and plants, infections, and autoimmune diseases" (Ifeanyi, *et al.* 2018).

Depending on where it originates, hepatitis may be mild and self-limiting or severe and need a liver transplant.On the basis of the duration of the liver's inflammation, hepatitis can be further defined as either acute or chronic. If liver inflammation lasts less than six months, it is named acute hepatitis; if it lasts more than six months, it is labelled chronic hepatitis. Depending on the aetiology, acute hepatitis can induce fulminant liver failure but often resolves on its own. On the other hand, chronic hepatitis may damage the liver and cause symptoms including; "liver fibrosis, cirrhosis, hepatocellular carcinoma, and portal hypertension", which can be fatal and cause significant morbidity. (Falade-Nwulia et al., 2020).

Some forms of hepatitis are preventable or treatable, but not others. Vaccination is the most effective way to protect against hepatitis A and hepatitis B. Treatments for hepatitis C are effective, but they can be expensive (Stanaway, *et al.* 2016).

The current investigation intends to evaluate the prevalence of hepatitis C virus in terms of age, gender, and geographic distribution, as well as to investigate the clinical kinds of this virus.

1- Hepatitis c

The Hepatitis C virus (HCV) is a dangerous human illness that is spread via the circulation of blood. There are around 120–130 million persons infected with HCV, which accounts for approximately 3% of the total population of the world. Infected hepatitis C virus refers to a serious public health concern because it is the causative agent of chronic hepatitis, which usually progresses to cirrhosis (Hollard *et al*., 2013) .

In the absence of treatment, the vast majority of acute infections will develop into chronic ones, and eventually lead to cirrhosis or HCC of the liver. Hepatocellular carcinoma and liver failure are both strongly associated with alcohol misuse and the metabolic syndrome (Alberti , 2009).

2- Chronic hepatitis C

Around 50%-85% of those who get the hepatitis C virus (HCV) will go on to develop chronic hepatitis after first infection. Many people with chronic hepatitis C may never develop any symptoms from the liver illness it causes. Cirrhosis is a condition that develops in 5 to 30 percent of people with chronic infection during a 20 to 30 year period. Chronic hepatitis C is the most common reason for chronic liver disease and liver transplants in the United States (Chopra et al., 2013).

Although many individuals with chronic hepatitis C infection experience symptoms, the majority of these symptoms are vague and are not definitely caused by HCV infection. Even when cirrhosis does occur, many people only have vague symptoms. Occasionally, individuals develop particular extra hepatic symptoms that are directly connected to HCV infection (such as cryoglobulinemia, renal illness, or certain dermatologic conditions) (Chopra et al., 2013).

3- Structure of hepatitis c virus

The Hepatitis C virus is a member of the Flaviviridae family and is classified as a tiny, encapsulated, positive single-stranded RNA virus. It is classified under the genus Hepacivirus. The viral spikes on the virion membrane are about 6 nm in size and are formed by heterodimers of E1 and E2 glycoproteins, according to the results of an evaluation of viruses that were isolated from plasma and the supernatant of cell cultures.Encapsulated particles are icosahedral and range in size from 56 to 65 nm, while the viral core is approximately 45 nm. Actually, the extracellular HCV particle population is very diverse. Size, buoyant density, and infectivity of the particles can all vary greatly (Gastaminza, *et al.* , 2010).

The vast majority of particles do not spread disease. The buoyant densities of infectious particles that have been recovered from blood and those that have been isolated from cell culture medium are both variable. HCV is unique because a high percentage of its particles are attached to lipoproteins in infected cells (Moriishi et al., 2012).

There are a number of lipoproteins that have been connected to HCV; they include low density lipoproteins (LDL), very low density lipoproteins (VLDL), and apolipoproteins (Apo) A1, B, C, and E. However, the pattern of virus-associated lipoproteins may vary. The term "lipoviral particles" was used to describe the viral particles that bind to lipoproteins. Low density lipoproteins (LDL), very low density lipoproteins (VLDL), and apolipoproteins (Apo) A1, B, C, and E are often linked to HCV. However, the pattern of lipoproteins linked to the virus can be different. "lipoviral particles"(LVP) are the name for the virus particles that are found in lipoproteins (Vercauteren, *et al.* , 2014).

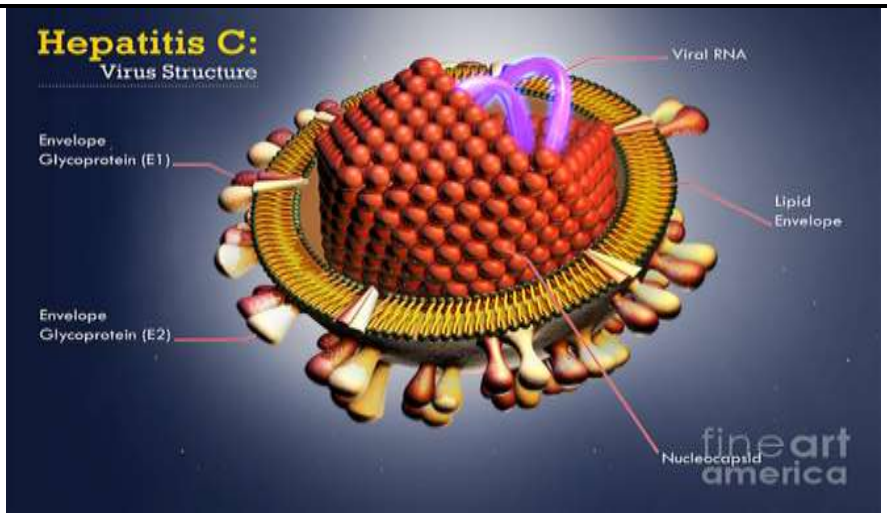


Figure 1.1: structure of hepatitis c virus (Moriishi et al., 2012)

4- Viral genome

The length of the HCV genome is calculated to be around 9600 nucleotides. It has one open reading frame (ORF) flanked by two highly conserved untranslated sequences (5'-UTR and 3'-UTR). Depending on the genotype, the ORF may comprise 9030 to 9099 nucleotides and encodes a single polyprotein precursor with 3010 to 3033 amino acids (aa). IRES at the 5' UTR initiates translation in the endoplasmic reticulum, where it occurs (Raney et al., 2010).

5- Viral protein

1. Core protein: Core protein is a structural protein that, when combined with other core proteins, forms the viral capsid. The viral genome is protected within the capsid, a spherical shell that encloses the virus. There are three structural HCV proteins: the core protein, the envelope glycoproteins (E1 and E2), and the viral spike protein. During nucleocapsid formation, the mature core protein helps the lipid membrane from the host connect to the HCV RNA. HCV genomic RNA is held by proteins at the N-terminal core (Kao, 2016).

2. E 1: The envelope glycoprotein E1-E2 is a highly glycosylated transmembrane protein made up of a pair of envelope glycoproteins E1 and E2 that are tightly bound together. Assembly, adhesion to the host cell, and fusing of the endosome membrane to the lipid bilayer are only a few of the roles performed by the E1 protein during the HCV replication cycle (Mazumdar, *et al.,* 2012).

3. E 2: The E2 envelope glycoprotein is a transmembrane protein that has undergone substantial glycosylation and forms heterodimers with the E1 envelope glycoprotein to form E1-E2 heterodimers. The HCV envelope consists of the E1-E2 heterodimers and the lipid membrane generated from the host. The host receptor's contact, entry, and fusion with the endosomal membrane are all facilitated by the elongated E2 protein (Freedman, *et al.,* 2016).

4. P 7: The viral assembly and release process involves the small, hydrophobic transmembrane protein p7. In contrast to popular belief, p7 does not make up the viral particle but instead has a structural function within hepatocytes. In the endoplasmic reticulum, the p7 proteins collaborate with other viral proteins to release core proteins from lipid droplets, which is required for capsid assembly and membrane envelopment (Denolly, *et al*., 2017).

5. NS2: The nonstructural protein 2 (NS2) of HCV functions as a cysteine protease and a cofactor throughout the assembly process. It's crucial for viral assembly coordination. Particularly, it seems that NS2 colocalizes with E1, E2, NS3, and NS5A close to the core proteins and lipid droplet during viral formation (Yi, *et al*., 2009).

6. NS3: The nonstructural 3 (NS3) protein is a bifunctional enzyme that may operate as both a serine protease and a helicase. The serine-type protease domain of NS3 is responsible for

catalysing the vast majority of the viral polyprotein cleavages that are necessary for the release of nonstructural proteins.Furthermore, NS3 is involved in evading the innate host immune response by the proteolytic inactivation of many host cell components that would otherwise prevent viral replication. The N3 helicase domain probably helps unwind viral RNA and promotes viral replication **(**Raney, *et al.* , 2010).

7.NS4A: The HCV nonstructural protein known as NS4A is the smallest of the nonstructural proteins that are produced by the virus. During the course of the HCV life cycle, the NS4A protein is responsible for a number of different functions. These include: (1) anchoring the NS3-4A complex to the outer leaflet of the endoplasmic reticulum and the mitochondrial outer membrane; (2) serving as a cofactor for the NS3A serine protease; (3) increasing the NS3A helicase activity; and (4) regulating NS5A hyperphosphorylation and viral replication. The connections between NS3 and NS4A contribute to viral assembly, whereas the contacts between NS4A and NS4B are responsible for regulating the process of genome replication (Phan, *et al*., 2011).

8. NS4B: Nonstructural protein 4B (NS4B) is a viral protein that mediates interactions between viruses and their hosts by inducing changes in the cytoplasmic membrane. This protein, together with other non-structural proteins, colocalizes to the endoplasmic reticulum and forms the replication complex (Lundin, *et al*., 2006).

9. NS5A: Nonstructural protein 5A(NS5A) is essential for HCV replication. NS5a interacts with NS4B, NS5B, RNA, and host cell proteins such cyclophilin A and kinases to coordinate viral replication and assembly.Efficient viral replication is facilitated by the NS5A protein's participation in the biogenesis of double-membrane vesicles (DMVs) in the endoplasmic reticulum (Romero, *et al*., 2015).

10. NS5B: The RNA-dependent RNA polymerase (RdRp) nonstructural protein 5B (NS5B) is essential for HCV replication. These enzymes play a crucial role in the replication of viral RNA by catalysing the polymerization of ribonucleoside triphosphates (rNTP) (Soriano, *et al.* , 2013).

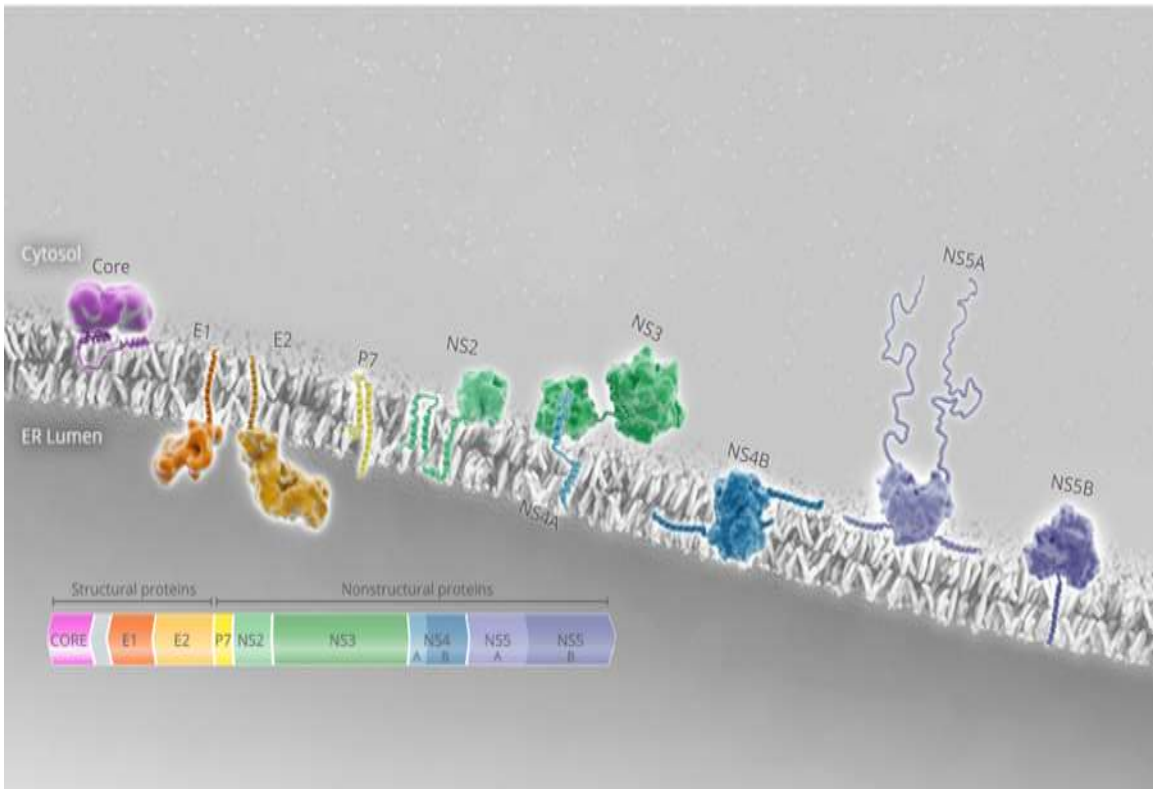


Figure1.2: Hepatitis c proteins(Soriano, *et al.* , 2013)

7- Hepatitis C virus life cycle

1.BINDING: HCV starts its life cycle by attaching to two hepatocyte receptors: low density lipoprotein receptor (LDLr) and heparin sulphate proteoglycans (HSPGs). It is at this point that the outer E1/E2 heterodimer membrane protein of HCV interacts to scavenger receptor B1 (SRB1) and the tetraspanin protein CD81. There is a wave in the lipid membrane caused by the interaction of these proteins. The HCV particle is carried to a hepatocyte tight junction through this wave (Lindenbach, *et al.,*2013).

2.ENDOCYTOSIS: Once HCV has reached the tight junction, CD81 will interact with claudin-1 (CLDN1), which will start the process of the viral particle and the hepatocyte cell membrane folding inward to form a pit-like area that will be covered by clathrin. The result of this procedure is an endosome enclosed by a clathrin cage, which contains a viral particle covered by the membrane of the host cell (Lindenbach et al., 2013).

3.FUSION AND UNCOATING: The clathrin cage that was surrounding the endosome and protecting it from the cytosol disassembles when a virus enters a cell, allowing the endosomal vesicle to be released into the cytosol. Endosomal fusion happens when the viral and host membranes fuse due to the endosomal environment's acidic pH. This triggers the release of HCV RNA from the capsid shell into the cytosol, where it may be translated and replicated (Lindenbach, *et al.*,2013).

4.TRANSLATION: Polyprotein translation from HCV RNA is initiated in the rough endoplasmic reticulum by the binding of ribosomal subunits to the RNA. This takes place during the translation process. To finish translating the HCV polyprotein, the ribosome-RNA complex binds to the endoplasmic reticulum membrane. At the end of the process, a single polyprotein with about 3,000 amino acids is made (Niepmann, *et al.,* 2018).

5.PROTEOLYTIC PROCESSING: The rough endoplasmic reticulum is the location of the proteolytic processing of viral proteins. The core, E1, and E2 proteins, as well as the p7 protein, are first cleaved by cellular proteases. The N-terminal end of NS3 protein then works with the NS2 cysteine protease to separate the two proteins. Finally, the remaining proteins are cleaved by an NS3-4A protease complex, which is formed when NS3 combines with membrane-bound NS4A. (NS3, NS4A, NS4B, NS5A, NS5B). Ten fully formed HCV proteins, including structural and nonstructural proteins, are the end product (Moradpour, *et al.,*2007).

6. RNA REPLICATION: Various HCV proteins, similarly in combination with host factors, remodel host cell membranes, causing double-membrane vesicle aggregation. Multiple copies of positive-sense progeny HCV RNA are created from a negative-sense RNA intermediate (template) synthesised by the NS5B RNA-dependent RNA polymerase in the membranous web. HCV RNAs that have just been generated are either employed for RNA translation and replication, or they are integrated into nucleocapsid particles. Several HCV nonstructural proteins help the RNA replication process forward (Kazakov, *et al*., 2015).

7. ASSEMBLY: Core proteins surrounding HCV RNA condense into the nucleocapsid near cytosolic lipid droplets (cLDLs) with the aid of the host diacylglycerol acetyltransferase-1 (DGAT1) enzyme.The HCV RNA serves as a template for the assembly process of the core proteins. In this way, the proteins encase the HCV RNA in a sturdy shield. After the core is established, the immature HCV particle fuses with an ApoE-loaded luminal lipid droplet (LuLD) to generate a dense HCV precursor.Accordingly, The endoplasmic reticulum (ER) also produces pre-very-low-density proteins (pre-VLDLs), which develop in the Golgi before being packed and released along with the high-density HCV precursor (Crouchet,*et al.* , 2017).

8.MATURATION: It is thought that pre-VLDLs merge with big triacylglycerol (TG)-rich lipid droplets in the Golgi to generate VLDLs. The HCV lipoviral particle is formed when the VLDLs combine with the high-density HCV precursors. As it travels out of the trans-Golgi network (TGN), this low-density HCV lipoviral particle is encased in multivesicular bodies. The cell's secretory machinery is responsible for transporting the multivesicular bodies to the cell surface. The endosomal-sorting complex

required for transport (ESCRT) pathway is required for multivesicular body formation as well as subsequent post-assembly processes leading to transport to the cell membrane and release of the lipoviral particle (Lindenbach, *et al.*, 2013).

9. RELEASE: The vesicles holding the HCV lipoviral particles fuse with the hepatocyte cell membrane once the particles are brought to the cell surface in multivesicular bodies. There is a simultaneous release of VLDL particles and HCV lipoviral particles into the extracellular space. This is because the synthesis of HCV lipoviral particles is related to the cellular VLDL particles (Coller, *et al.,* 2012).

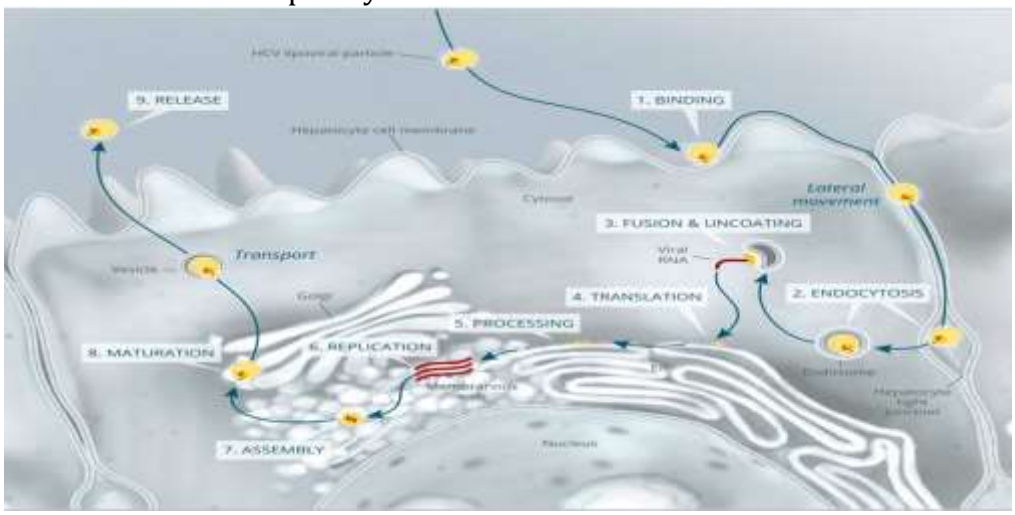


Figure ()Hepatitis C virus life cycle (Coller, *et al.,* 2012)

8-Pathogenesis:

The non-cytopathic hepatitis C virus simultaneously initiates replication after entering a liver cell and beginning its infection of that cell. This results in cell death in different ways including; "immune-mediated cytolysis and hepatic steatosis, oxidative stress, and insulin resistance". The HCV genome is divided into many sub-genomic sections, each of which codes for a protein or peptide (Irshad, *et al.*,2006).

Blood circulation is the route through which the hepatitis C virus (HCV) enters the liver and causes infection. In order to infiltrate cells, HCV isolates need at least four host-derived factors, including scavenger receptor class B type I, Occludin, Claudin-I (CLDNI), and CD81. It has also been established that CLDN6 and CLDN9 may stand in for CLDN1 as HCV entrance factors in human cells other than liver cells (Haid, *et al.*,2014).

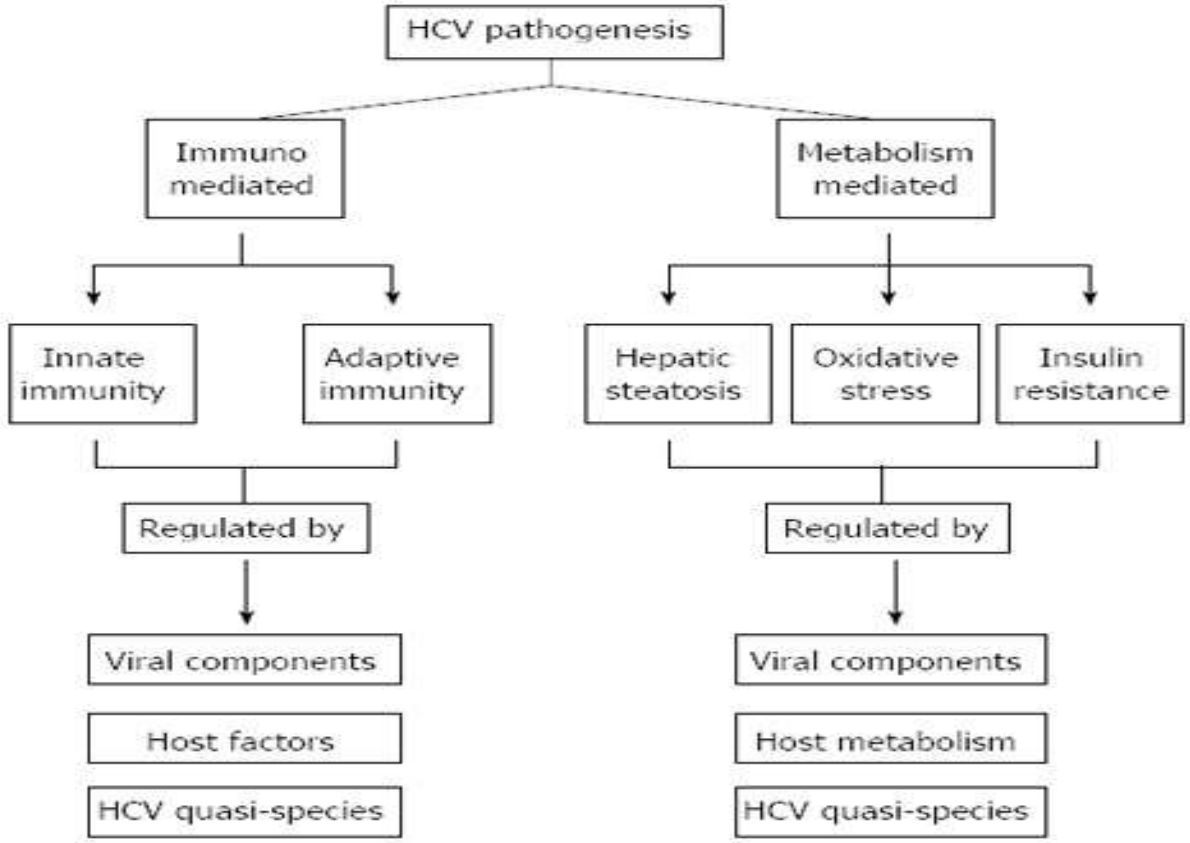
Viral entrance into liver cells is facilitated by the CD81 molecule on host cell surfaces, which functions as a viral receptor and connects with the viral particle. CD81 forms complexes with other cell-surface receptors, notably CD19 and CD21 on B cells, to provide costimulatory signals to the cells. The cells react to the stimulus. E2, a protein on the surface of viruses, interacts with CD8's main extracellular loop. (Zeisel, *et al.*,2013).

Figure1.4: Host immunity and metabolic variables influence hepatitis C virus pathogenesis(Haid, *et al.*,2014)

The hepatitis C virus is capable of attaching to several sites and has the potential to attach itself to a broad range of molecules. Some of these molecules include the low-density lipoprotein receptor, the intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN), and its liver homologue. Strain-specific interactions between E2 and CD81 have been documented since E2 is the viral protein with the greatest degree of variability (Haid, *et al.*,2014).

Two of its highly variable regions (HVR-1 and HVR-2) are constantly changing, most likely in response to virus-neutralizing antibodies and HCV-specific cytolytic T cells (CTLs). The inability of HCV's RNA-dependent RNA polymerase to act as a proofreader contributes to the virus's high mutation rate. So, an infected person will house many species of the Hepatitis

C virus, all of which are related but unique. HCV quasispecies are the name for these species (Haid, *et al.*,2014)



9- Symptoms

Chronic hepatitis C, which is a long-term infection with hepatitis C, is often a "silent" illness for many years until the virus does enough damage to the liver to cause symptoms. These symptoms include the following:

- Easy Bleeding
- Easy Bruising
- Fatigue
- lack of appetite
- Skin and eyes that are yellow (jaundice)
- Dark-colored urine
- Itchy skin
- Fluid accumulation in your abdomen (ascites)
- Swelling in your legs
- Lossing Weight
- Hepatic encephalopathy, commonly characterised as confusion, sleepiness, and slurred speech
- Blood tubes on your skin that resemble spiders (spider angiomas) (Herrera et al., 2018)

10- Epidemiology of Chronic Hepatitis C

The number of persons infected with the chronic form of hepatitis C virus is believed to be between 130 and 170 million, or around 3 percent of the global population. More than 350,000 individuals worldwide lose their lives each year due to complications associated with hepatitis C. The combination of IDU and intravenous drug use led to a dramatic rise in rates in the 20th century.

Infectious drugs or inadequately sterilised medical equipment. It has been shown that Egypt has the highest global HCV prevalence. Although the reason for this differential is uncertain, consistently infected males have a 10% to 15% chance of developing cirrhosis, whereas persistently infected females have a 1% to 5% risk. Cirrhosis progresses at a slower pace after it has been established.

Hepatocellular carcinoma occurs at a rate of 1% to 4% every year (Yu et al., 2009). Some African and Asian nations have a greater prevalence. Egypt (22%), Pakistan (4.8%), and

China (3.2%) have relatively high infection rates. The high rate of schistosomiasis in Egypt is suspected to be related to a mass treatment effort that continues to this day despite the fact that it employs poorly sanitised glass syringes. (Ifeanyi *et al*., 2018).

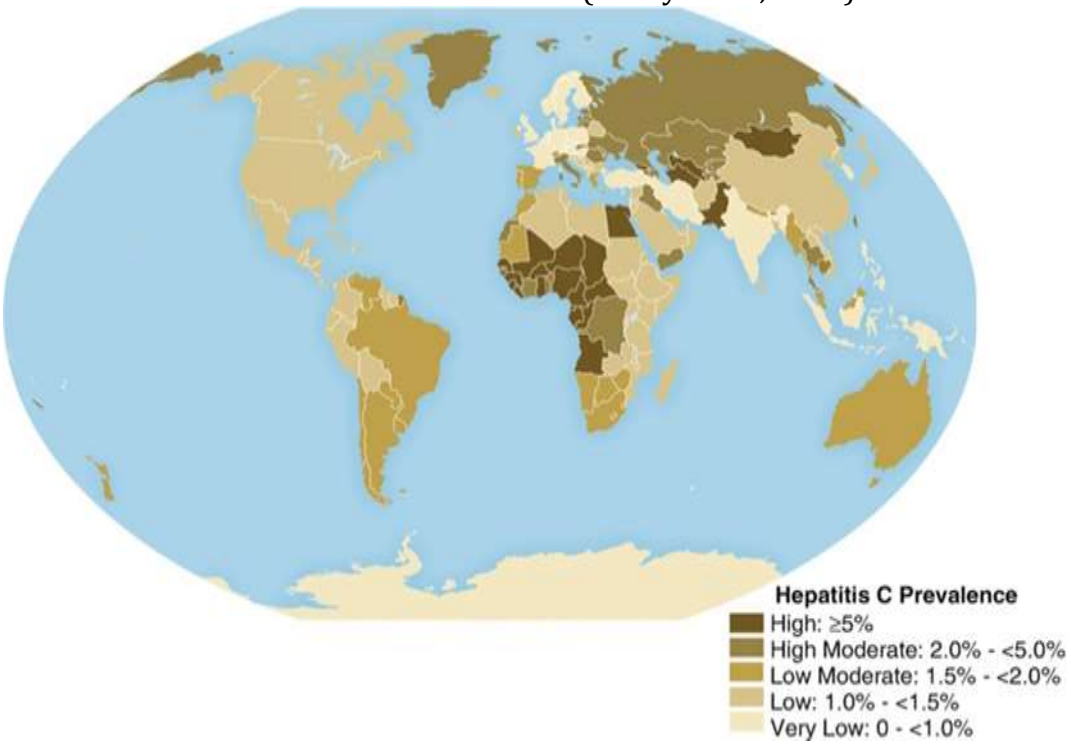


figure 1.5: Global Epidemiology of Chronic Hepatitis C Virus(Yu et al., 2009).

11- Diagnosis

Serologic tests, which identify human antibodies created in response to hepatitis C virus (HCV) infection, are employed as the first method for diagnosing hepatitis C infection (Getchell, *et a.,*2013).

One of the following three situations may be inferred from a positive HCV antibody test: either an ongoing infection, a cured prior HCV infection, or a false-positive test. These anti-HCV antibody assays are unable to distinguish between acute (new), chronic, and absent infections (Yu et al., 2009*).*

- Enzyme Immunoassay (EIA): Antibodies associated to recombinant antigens created from four different areas of HCV are what the third-generation HCV EIA is looking for (core, nonstructural 3, nonstructural 4, and nonstructural 5).A positive or negative result from the EIA test is provided when the absorbance signal is above or below a predetermined threshold.
- Chemiluminescence Immunoassay (CIA): The CIA test is an antibody test similar to the EIA, however it is employed less often than the EIA.The CIA and the third-generation EIA are both good at figuring out if someone has HCV(Alter,*et al.,*2003).
- Point-of-Care Rapid Immunoassays: In 2010, the Food and Drug Administration (FDA) of the United States gave its approval for the OraQuick HCV Rapid Antibody Test to be used as a point-of-care test using whole blood samples. These samples may be collected either venipuncture or by using a fingerstick. For the first HCV antibody test, this OraQuick Rapid Antibody Test can be used instead of the third-generation EIA (Lee, *et al*.,2011).
- Recombinant Immunoblot Assay (RIBA): The RIBA test detects specific antibodies produced in response to HCV antigens and is classified as positive (two or more antigens), ambiguous (one antigen), or negative (0 antigens) (Kumar,*et al.,* 2018).

12- Treatment

Antiviral medications

Drug used to treat hepatitis C aim to completely wipe out the virus in the patient's system. After 12 weeks without detectable hepatitis C virus in

the body, treatment is considered successful. Researchers have lately achieved substantial advancements in hepatitis C therapy by using new, "direct-acting" antiviral medicines, which are often used in conjunction with current ones. As a consequence, patients receive improved results, fewer side effects, and shorter treatment durations, with some treatments lasting as little as eight weeks. The genotype of the hepatitis C virus, the degree of liver damage, any other underlying medical conditions, as well as any past treatments, all have a role in the choice of medications and the length of treatment (Mayberry et al., 2019).

Liver transplantation:

Liver transplantation can be a possibility if your persistent hepatitis C infection has caused severe problems. During a liver transplant, your diseased liver is removed and replaced with a healthy liver. Liver transplants typically use organs from dead donors, although sometimes organs from living donors are used.

Hepatitis C cannot be cured by a liver transplant alone in the majority of instances. It is probable that the infection may recur, necessitating therapy with antiviral medicine to avoid liver damage. Several studies have shown that new direct-acting antiviral drug regimens can cure hepatitis C after a liver transplant. In addition, prior liver transplantation, therapy with direct-acting antivirals may be performed in carefully chosen individuals.(Mayberry et al., 2019)

13- Vaccine

There is presently no vaccination available, however numerous vaccines are being developed. The majority of vaccinations function by eliciting an immune response that attacks the viruses' outer membranes. However, developing an efficient vaccination against HCV is challenging since the virus is very diverse across strains and quickly mutates.(Verma,*et al.,*2014)

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