

Article Review: The Hepatic Physiology and Pathophysiology of Different Types of Hepatitis

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ABSTRACT

Globally, viral hepatitis is a frequent cause of liver disease with high morbidity and fatality rates. Since the liver produces a large number of hematopoietic factors and carries out numerous essential tasks that influence metabolism throughout the body. The purpose of this study is to identify hematological complications in patients with acute viral hepatitis. This information will be useful for treating and monitoring these patients. Also, everyone should be aware of the symptoms of hepatitis. Due of this, this article.

Keywords- Liver, Cirrhosis, Hepatitis, Characteristics of hepatitis viruses.

I. INTRODUCTION

The liver is the largest solid organ, the largest gland, and one of the most important organs in the body, serving as a centre for nutrient metabolism and waste metabolite excretion (Ozougwu and Eyo,2014). The liver is about 1500g in weight and accounts for about 2.5 percent of adult body weight. The liver's surface is smooth and dome-shaped, and it is related to the concavity of the diaphragm's inferior surface. The liver is mostly hidden and protected by the thoracic cage and diaphragm in the right upper quadrant of the belly. On the right side, the normal liver is deep to the ribs 7–11 and crosses the midline towards the left nipple (Guyton and Hall, 2016). The falciform ligament divides the liver into two lobes: a bigger right lobe and a smaller left lobe. The liver is connected to the anterior abdominal wall via the falciform ligament. At its base, the ligamentum teres, which houses a piece of the vestige umbilical vein, the right and left hemi livers are further divided into a total of eight segments, each with its own hepatic artery branches and biliary tree, based on the divisions of the hepatic and portal veins. Under the protective covering of the lower

ribs, the right upper quadrant (hypochondrium) of the abdominal cavity is divided into numerous smaller units called lobules, each of which is made up of a single liver cell (hepatocyte) plate, a central vein, radiating sinusoids, and peripheral portal tracts. (Sibulesky,2013). Hepatocyte sheets line the inside of the liver and extend outward like spokes of a wheel. The hepatocytes produce bile, which is collected by bile canaliculi, and blood sinusoids, which carry blood through lobules. (Ozougwu and Jevas,2017). The central vein in the center of a liver lobule, which is supplied by branches of the hepatic artery and branches of the portal vein, is where blood enters a liver lobule at its outer aspect, travels inward through the sinusoids, and exits the lobule. Bile flows outward into the bile canaliculi into the bile ducts, which drain into progressively larger ducts, eventually into the common bile ducts, which carries the bile to empty into the duodenum. The hepatic vein joins the central veins of the lobules to form the hepatic vein, which transports blood away from the liver to the heart. (Parveen and Michael,2006).On the other hand this vital organ functions as an exocrine gland that secretes bile into the intestine, as well as an endocrine gland and a blood filter. The liver is a metabolic factory

that synthesizes and degrades a wide range of compounds. It's a very active organ (Guyton and Hall, 2011). A complete loss of liver function can result in death in minutes, highlighting the liver's critical role (Ozougwu, 2014).

II. MAJOR HEPATIC FUNCTIONS

2.1 *metabolism of lipids, proteins, and carbs:*

Particularly important for preserving a healthy blood glucose level is the liver. The liver's ability to act as a glucose buffer enables it to remove extra glucose from the blood, store it, and then release it back into the blood when the blood glucose concentration starts to drop too low. Gluconeogenesis in the liver is essential for maintaining a normal blood glucose concentration since it only occurs to a significant degree when the blood glucose concentration goes below normal. The subsequent conversion of large amounts of amino acids and glycerol from triglycerides to glucose permits blood glucose levels to stay essentially normal. (Guyton and Hall, 2016).

The liver's main functions in lipid metabolism are to synthesis triglycerides, largely from carbohydrates but also to a lesser extent from proteins, breakdown fatty acids into tiny energy-producing molecules, and synthesize other lipids from fatty acids, particularly cholesterol and phospholipids. In addition to triglycerides, the liver cells contain vast amounts of phospholipids and cholesterol, which are constantly generated by the liver. Furthermore, because liver cells are significantly more capable of desaturating fatty acids than other tissues, liver triglycerides are generally much more unsaturated than adipose tissue triglycerides. Because the liver is the main source of unsaturated lipids, which are found in considerable levels in many structural components of all cells, the capacity of the liver to desaturate fatty acids is functionally important to all bodily tissues. A dehydrogenase in the liver cells accomplishes this desaturation. The liver is in charge of a large portion of fat metabolism. The liver converts about 80% of the cholesterol it produces into bile salts, which are then discharged into the bile; the other 20% is transported by lipoproteins and circulated throughout the body's tissue cells. Also produced in the liver, phospholipids are predominantly transported via lipoproteins. Cholesterol and phospholipids are used by cells to create membranes, intracellular structures, and a number of chemical molecules necessary for cellular activity. The liver is responsible for almost all of the body's fat synthesis from carbs and proteins. Lipoproteins transport fat from the liver to the adipose tissue where it is stored. (Guyton and Hall, 2011). Also the liver produces plasma proteins such as albumins and globulins (with the exception of gamma-globulin). Aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase are among the non-essential amino acids and serum enzymes synthesized by the liver (Ozougwu and Jevas, 2017).

2.2 *Metabolism of bilirubin*

Bilirubin and bile salt metabolism, as well as the metabolism of medications and alcohol, all take place in the liver. It is involved in the breakdown of aged red blood cells, which produces bilirubin as a by-product. Bilirubin is divided into two categories (fat-soluble and water-soluble) (Alexander and Kourtis, 2007). The body must discard fat-soluble bilirubin, which is transported in the plasma attached to a protein because it is toxic to cells. Nevertheless, in the hepatocytes, unconjugated bilirubin is converted to conjugated bilirubin, a less toxic water-soluble version. This is a component of bile that is discharged into the duodenum via the common bile duct from the bile channels in the liver lobules (Marshall, 2000).

Some bile is kept in the gall bladder and released into the stomach when needed for digestion, while the remainder flows into the gut via the common bile duct. The hepatic duct is generated when numerous small bile channels unite to make the hepatic duct. (Huether, 2000). In the gut, conjugated bilirubin is transformed into urobilinogen, which is primarily removed as stercobilin in the stool. Some urobilinogen is reabsorbed into circulation and excreted in the urine. (Marshall, 2000). Hepatocytes produce 600–1200 ml of bile every day, which is important for the gut's absorption of fat-soluble vitamins and the breakdown of dietary fats. (Porth, 2002).

2.3 *Vitamin and mineral metabolism and storage:*

Certain vitamins, such as vitamin B12, D, E, and K, are stored in the liver. (Huether, 2000). Some vitamins, like A and D, are stored in considerable amounts by the liver, while others, like vitamin K and folate, are kept in lower amounts and evaporate quickly if dietary intake is inadequate. It's also important for the metabolism of vitamin D and vitamin K. (important for the production of coagulation factors II, VII, IX, and X in the liver) (Mark, *et al.*, 1998). Minerals like copper and iron (in ferritin and hemosiderin forms) are stored in the liver (Nicholas, *et al.*, 2006). Vitamin A may be stored in sufficient levels to avoid insufficiency for up to ten months. While vitamin B12 can be kept in storage for at least a year, if not several years, vitamin D can only be retained in sufficient quantities to prevent deficiency for 3 to 4 months.

2.4 *Detoxification function*

The liver is one of the most important organs in the body. The liver is responsible for hundreds of tasks, including the processing of nutrients and hormones, as well as the removal of waste products produced by regular physiological operations. Farm chemicals, air pollutants, and chemicals from personal care items are examples of external toxins (naturally occurring) and toxicants (man-made) that the liver helps to break down and remove. Medications, both prescription and over-the-counter, Food additives, colorings, taste enhancers, preservatives, and artificial sweeteners, as well as alcohols and volatile organic compounds found in scents and air fresheners. The Cytochrome P450 family of enzymes is responsible for Phase I's function. These enzymes aid in the

neutralization of drugs like caffeine and alcohol, as well as the conversion of chemicals into forms that are easier to eliminate from the body. However, if these harmful intermediates are allowed to accumulate, they can harm DNA and proteins. The aim of Phase II liver detoxification is to help neutralize these intermediates and convert them into chemicals that can be eliminated by the body through a process called conjugation (Sears and Genuis,2012).

III. LIVER CIRRHOSIS

Cirrhosis of the liver is the 12th most prevalent cause of death in the US. It was the cause of 29,165 fatalities in 2007, with a mortality rate of 9.7 per 100,000 people. The incidence of hepatocellular carcinoma tripled between 1975 and 2005 as a result of cirrhosis, a significant risk factor for the disease (Park *et al.*,2013).

3.1. Clinical presentation

Since ancient times, the clinical signs of cirrhosis have been understood. Ascites is described in the Ebers papyrus, which was written approximately 2600 BC. Ascites was formerly thought to be related to a hardened liver and heavy alcohol consumption. Decompensated cirrhosis is characterized by abdominal enlargement, jaundice, and gastrointestinal bleeding. (Nagahara *et al.*,2010). Physical examination findings include a constricted, nodular liver, splenomegaly, ascites, dilated abdominal wall veins, spider angioma, palmar erythema, peripheral edema, and asterixis. The sensitivity of these signs ranges from 31 to 96 percent (Lid sum *et al.*,2005). Laboratory results may accidentally diagnose patients. Alanine transaminase and aspartate transaminase levels that are elevated in the liver are indicative of continuous hepatocyte injury, but they may be normal in cases of severe liver disease (Tacke *et al.*,2011) A diminished ability of the liver to produce clotting factors may be indicated by an increase in serum prothrombin time or the International Normalized Ratio (INR). Splenic sequestration may be indicated by thrombocytopenia. There may also be an increase in total bilirubin. Although nonalcoholic fatty liver disease is becoming a more significant cause of cirrhosis, alcohol abuse and viral hepatitis are still the most frequent causes (Hwang and Lee, 2011)

3.2. Pathophysiology

Chronic liver disease with associated hepatocyte death results in inflammation followed by fibrosis, as evidenced by elevated serum transaminase levels (Koike and Moriya,2005). The liver loses its capacity to manufacture proteins like clotting factors and transaminases as hepatocytes die, which can cause the serum bilirubin level to rise and cause an increase in INR (which then may appear at normal or low levels). Pressure inside the portal system increases as the fibrosis worsens, causing platelet sequestration in the spleen and the development of esophageal varices (Tanaka *et al.*,2008)

3.3 Diagnosis of liver cirrhosis

In many cases, cirrhosis or its consequences are present. The degree of fibrosis can be estimated using biomarkers including type I and type III collagen, laminin, and hyaluronic acid, even if liver biopsy remains the "imperfect" diagnostic standard (owing to sample error). The Fibro Sure biomarker assay has a sensitivity of 85% and a specificity of 72.2% for detecting hepatic fibrosis. The severity of fibrosis can also be determined by clinical signs, such as a combination of transaminase tests, platelet count, and age. Fibrous septa between the portal fields, which can be micro- or macronodular, are what histologically characterize cirrhosis. Clinical examination, laboratory tests, and auxiliary studies are used to diagnose the illness. Skin-deep indications of liver disease, a firm liver when touched, and a few risk factors like metabolic syndrome, binge drinking, and exposure to hepatotoxic drugs are all indicators of cirrhosis. Hepatotoxic medication uses Early signs of cirrhosis in B-ultrasonography include hepatic tissue inhomogeneity, irregularity of the hepatic surface, and caudate lobe enlargement. Portal hypertension is the root cause of splenomegaly. Thrombocytopenia, impaired hepatic biosynthesis (as shown by low albumin and cholinesterase concentrations and an increase in the international normalized ratio [INR]), and impairment of the liver's detoxifying function (as shown, for example, by elevated bilirubin concentration) are all present in advanced liver disease on the verge of cirrhosis. Transaminase concentrations were generally normal or only slightly elevated. There is no well-defined laboratory test threshold value that can be used to determine when cirrhosis screening should be performed. Upper abdominal ultrasonography and gastroscopy are examples of ancillary studies. EGD is a procedure that should be carried out anytime cirrhosis is first identified or suspected because it can be used to show esophageal varices and evaluate the likelihood that they will bleed. It is either unnecessary or perhaps hazardous to biopsy the liver. if cirrhosis has been definitively diagnosed based on clinical signs and imaging tests (e.g., evidence of decompensation, with ascites and impaired hepatic biosynthesis).If the etiology of liver disease is unknown or the stage cannot be determined by the above-mentioned tests, a liver biopsy is recommended Transcutaneous liver biopsy is recommended in patients of suspected cirrhosis if the clinical findings raise questions about the diagnosis or if the biopsy is anticipated to reveal information about the cirrhosis's etiology that may influence the choice of treatment. To accurately stage hepatic fibrosis, the liver biopsy punch cylinders must be at least 15 mm long and at least 10 portal fields must be examined each sectional level. It should be remembered that histological detection of the initial underlying cause may be challenging or impossible once liver disease had progressed to the point of cirrhosis. (Herbig *et al.*,2014).

3.4. Non-invasive cirrhosis diagnosis testing

Recently, a number of laboratory- and ultrasound-based techniques for the non-invasive diagnostic assessment of cirrhosis have been developed. Since the only question to be answered is the stage of fibrosis, these noninvasive techniques frequently eliminate the necessity for liver biopsy; however, the information they provide must always be taken into account in light of the concomitant clinical symptoms. There are two types of laboratory-based techniques for determining the degree of hepatic fibrosis: those based on standard liver function tests and those based on specific laboratory values that are linked to fibrosis, including the hyaluronic acid content. The AST-to-platelet ratio index (APRI), which can be used to screen for advanced fibrosis and cirrhosis, is simply calculated as the ratio of the AST (GOT) and the platelet count. The basis for the diagnosis of cirrhosis is the correlation between the level of fibrosis and the degree of liver stiffness as determined by ultrasonography. For the staging of fibrosis in various liver disorders, transient electrography and the acoustic radiation force impulse (ARFI) approach are now well-established techniques. These two techniques can be performed repeatedly on an outpatient basis, and they can also be combined. Techniques for the measurement of liver stiffness and laboratory indices of hepatic fibrosis enable longitudinal assessment of the progression and regression of fibrosis in patients with chronic liver disease (Machida *et al.*,2009).

IV. HEPATITIS

Hepatitis is a term that refers to inflammation of the liver tissue in general. It can be caused by a variety of factors, the most common of which is a viral infection. Hepatitis viruses infect roughly 2.3 billion individuals worldwide, resulting in 1.4 million deaths each year (Chayanupatkul and Liangpunsakul.,2014). Microscopic examination reveals broken liver cell cords, patchy parenchymal cell degeneration, and necrotic hepatocytes. Along with these parenchymal changes, there is also reticuloendothelial (Kupffer) cell hyperplasia, periportal

mononuclear cell infiltration, and cell disintegration. In small, compact areas, necrosis frequently happens. There is an increase of macrophages around degenerating hepatocytes later in the course of the disease. The reticulum framework is preserved, allowing hepatocyte regeneration and the restoration of the liver lobule's highly organized architecture. In 8–12 weeks, the injured hepatic tissue is usually recovered (Carroll *et al.*,2016). Hippocrates was the first to coin the term "hepatitis" (460-375 BC) Martin described a non-fatal variant of infectious hepatitis among military personnel in 1918., while in 1943 Beeson's account of cases of jaundice resulting from whole blood transfusion, and at the same year the 1943 Cameron's report of an epidemic hepatitis among troops during World War II. (Lawrence, 2010). Although viral hepatitis accounts for over 90% of instances, it can also be caused by non-viral causes such as alcohol addiction, autoimmune disease, or pharmaceutical usage. Alcoholic hepatitis is produced by the metabolism of ethanol and is connected with long-term alcohol intake (the chemical term for alcohol) Autoimmune hepatitis occurs when the body's immune response produces autoantibodies, ingesting a hazardous dose of medications causes medication-induced hepatitis. It occurs when the liver is damaged as a result of the medicine being broken down in the bloodstream. Some drugs, such as acetaminophen (paracetamol), cause liver damage over time, while others, like acetaminophen (paracetamol), can cause hepatitis after a single overdose (Jefferies *et al.*,2018). In most cases, hepatitis is a non-discriminatory infection. The infection isn't limited to a narrow social, geographical, or economical location, even if each type may target a certain group of people (who.,2011).

V. CHARACTERISTICS OF HEPATITIS VIRUSES

The characteristics of the five most well-known hepatitis viruses were explained in Table (1). Table (2) explains the nomenclature of hepatitis viruses, antibodies, and antigens, and Table (3) lists the clinical characteristics of viral hepatitis types A, B, and C.

Table (1): Characteristics of hepatitis viruses (Carroll *et al.*, 2016).

Virus	Hepatitis A	Hepatitis B	Hepatitis C	Hepatitis D	Hepatitis E
Family	Picornaviridae	Hepadnaviridae	Flaviviridae	Unclassified	Hepeviridae
Genus	<i>Hepatitisvirus</i>	<i>Orthohepadnavirus</i>	<i>Hepacivirus</i>	<i>Deltavirus</i>	<i>Hepevirus</i>
Virion	27nm,icosahedral	42nm, spherical	60nm,spherical	35nm, spherical	30-32nm, icosahedral
Envelope	No	Yes (HBsAg)	Yes	Yes (HBsAg)	No
Genome	ssRNA	dsDNA	ssRNA	ssRNA	ssRNA
Genome Size (Kb)	7.5	3.2	9.4	1.7	7.2
Transmission	Fecal-oral	Parenteral	Parenteral	Parenteral	Fecal-oral
Prevalence	High	High	Moderate	Low, regional	Regional

Stability	Heat and acid stable	Acid sensitive	Ether sensitive, acid sensitive	Acid sensitive	Heat stable
Fulminant Disease	Rare	Rare	Rare	Frequen	In pregnancy
Oncogenic	No	Yes	Yes	?	No
Chronic disease	Never	Often	Often	Often	Never

Table (2): Nomenclature and definitions of hepatitis viruses, antigens, and antibodies (Carroll *et al.*, 2016).

Disease	Component of system	Definition
Hepatitis A	HAV	Hepatitis a disease. Etiologic agent of infectious hepatitis. the first member of the genus Hepatovirus, a picornavirus.
	Anti-HAV	HAV antibody. With the first sign of symptoms, detectable; lifelong persistence.
	IgM anti-HAV	HAV-specific IgM antibody. Up to 4-6 months after infection, a positive test indicates a recent hepatitis A infection.
Hepatitis B	HBV	virus that causes hepatitis B. serum hepatitis' etiologic cause. a hemovirus.
	HBsAg	Surface antigen for hepatitis B. Several subtypes of HBV surface antigens have been found, with high levels of detection in serum.
	HBeAg	Antigen for hepatitis B. circulating as a soluble antigen in serum, associated with the HBV nucleocapsid, and indicating viral replication.
	HBcAg	core antigen for hepatitis B.
	Anti-HBs	anti-HBsAg antibody. indicates the presence of a passive HBIG antibody, a prior HBV infection and immunity, or an HBV vaccine-induced immune response.
	Anti-HBe	anti-HBeAg antibody. The presence of HBsAg carriers in serum signifies a lower HBV titer.
	Anti-HBc	anti-HBcAg antibody. indicates a prior HBV infection at an arbitrary time.
Hepatitis C	HCV	The common etiologic agent of post-transfusion hepatitis is the hepatitis C virus. Hepacivirus is a kind of flavivirus.
	Anti-HCV	HCV antibody.
Hepatitis D	HDV	The hepatitis D virus. Only when HBV is present does the etiologic agent of delta hepatitis produce infection.
	HDAg	Antigen delta (Delta-Ag). Early acute HDV infection is detectable.
	Anti-HD	Anti-delta-Ag antibody (anti-delta). indicates an HDV infection, either current or previous.
Hepatitis E	HEV	viral hepatitis E. Hepatitis virus spread by enteric contact. generates significant outbreaks in Mexico, North and West Africa, and Asia. transmission by water or through feces. a Hepe virus.

Table (3): Epidemiologic and clinical features of viral hepatitis types A, B and C (Carroll *et al.*, 2016).

Feature Viral Hepatitis	Hepatitis A virus	Type B Viral	Type C
The gestation period	10-50 days (average, 25-30)	50-180 days (average, 60-90)	15-160 days (average, 50)
Route of infection	mostly oral-fecal	mostly parenteral	mostly parenteral
Principal age distribution	youngsters, adults, and children	15-29 years and babies	Adults
Periodic occurrence	Throughout the year, with an autumnal peak.	The entire year	The entire year

Occurrence of virus			
Blood	2 weeks before to ≤1 week after jaundice	Months to years	Months to years
Urine	Rare	Absent	Probably absent
Stool	2 weeks before to 2 weeks after jaundice	Absent	Probably absent
Saliva, semen	Rare (saliva)	Frequently present	Present (saliva)
Clinical and laboratory features			
Onset	Abrupt	Insidious	Insidious
Duration of aminotransferase elevation	1-3 weeks	1-6+ months	1-6+ months
Fever >38°C	Common	LessCommon	LessCommon
Immunoglobulins (IgM levels)	Elevated	Normal to slightly elevated	Normal to slightly elevated
Mortality rate	<0.5%	<1-2%	0.5-1%
Complications	Uncommon, no chronicity	Chronicity in 5-10% (95% of neonates)	Chronicity in 70-90%
HBsAg	Absent	Present	Absent
Immunity			
Homologous	Yes	Yes	No
Heterologous	No	No	No
Duration	ifetime	ifetime	Ifetime
Ig intramuscular (IG, γ-globulin, ISG)	Regularly prevents jaundice	Prevents jaundice only if immune globulin is sufficient potency against HBV	Prevents jaundice only if immune globulin is sufficient potency against HCV

Hepatitis is a word used to denote inflammation of one of the key organs, the liver which conducts numerous critical processes pivotal to metabolism throughout the body in adds to synthesis of erythropoietin, thrombopoietin, plasma proteins and clotting factors. Several different hematological conditions are linked to liver disease. Anemia can develop from a variety of factors, including altered red cell lipid metabolism and disrupted hemoglobin metabolism. Due to the impact of liver illness, platelet number and function are both compromised. (Bader and Enaam,2016). Hepatitis can have a variety of causes, some of which are contagious and others not. Hepatitis is frequently caused by viruses (A, B, C, D, E, and G), which infect millions of people worldwide and cause significant morbidity and mortality. (Cotran *et al.*,2004). Although HCV causes more than 50% of current liver transplants and is the most common cause of cirrhosis. (Mitruka,2014).

VI. VIROLOGY

6.1. Viral Hepatitis Type C (HCV)

All nations are affected by the serious global health issue of hepatitis C. (Lavancy,2011). Over 180 million people, or 2% of the world's population, are said to be veneremic (Saraswat *et al.*,2015) Data on the incidence of new cases, however, is challenging to find

because the majority of acute hepatitis C virus (HCV) infections remain asymptomatic. (Cower *et al.*,2014). Just 10% of individuals affected have received a diagnosis, and only 50% of those who have received therapy have seen a durable virological response (SVR) (Gane *et al.*, 2014). About 75% of infected people are unaware of their condition, and of those, 70% to 85% will not be able to get rid of the virus and will continue to be sick for a long time. When a person has a chronic infection, some of them will gradually acquire advanced liver disease while mainly remaining asymptomatic until liver cirrhosis and hepatocellular cancer appear (Hatzakis *et al.*,2014). Direct antiviral therapies are extremely effective yet costly. 90% of patients achieved SVR, patients with decompensated cirrhosis had much lower SVR, although this was unaffected by insurance status or alcohol or drug use, and there is a lack of real-world efficacy in vulnerable populations, particularly uninsured patients. Directly acting antivirals (DAAs) have revolutionized how chronic hepatitis C (HCV) is managed. Loss to follow-up, viral relapse, non-treatment-related mortality, and treatment termination of patients with viral relapse, reported non-compliance, and had not been retreated were the causes of treatment failure. (Christina *et al.*, 2017).

6.1.1 The epidemiological review about HCV

Particularly in HIV-positive individuals receiving active antiretroviral therapy, chronic HCV

infection is frequently linked to the development of liver cirrhosis, hepatocellular carcinoma, liver failure, and mortality. (Antiretroviral.,2010). While the frequency of HCV infection appears to be declining in the industrialized world, it is predicted that over the next 20 years, mortality secondary to HCV infection will continue to rise (Razavi *et al.*, 2013) A thorough understanding of HCV infections should therefore be necessary to design measures to avoid new infections, even though numerous statistics indicate that HCV infection could be eradicated in the next 15 to 20 years with focused therapy techniques. (WHO, 2017) Discovered in 1989.(Beghdadi *et al.*,2009) The Flaviviridae family, which also includes a number of arthropod-borne human infections of the Flavivirus genus like the yellow fever virus, is home to the positive sense, single stranded RNA virus known as HCV. Dengue and West Nile viruses. The GBV-B virus, the HCV genome organization, and the recently discovered non-primate, rodent, and bat hepaciviruses are all shown in figure 1. Hepacivirus is the genus in which HCV has been placed. (LoB *et al.*, 2011; Yahia, 2011 and Tabll *et al.*, 2011). Seven genotypes and a number of subtypes of HCV isolates have been identified, each with a unique geographic distribution and sensitivity to interferon-based therapy. (Paez *et al.*,2011) The chimpanzee is the only genuine HCV animal model, and it is essential for research on HCV immunity and pathogenesis. (Hanafi *et al.*, 2011).

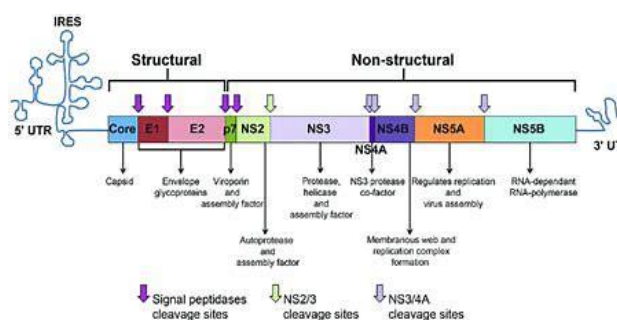


Figure (1): HCV genome and proteins

Furthermore, genetically altered and human-liver chimeric mice models that are permissive to HCV have also been created. (Esmat *et al.*,2011) The absence of a cell culture method has long been a significant barrier to understanding the HCV life cycle. To comprehend HCV genomic replication and virus entry, however, selectable replicon systems and retrovirus-based pseudo typed particles have become crucial tools (Lavanchy, 2011)

Eventually, since 2005, complete viral replication systems have made it possible to analyze the entire viral life cycle (Shepard *et al.*,2015). It should be emphasized that these cell culture methods mainly use HuH-7-derived hepatoma cells. However, this cell line lacks a lot of the characteristics of hepatocytes. (Strickland,2016). Thus, primary human hepatocytes or human liver slices have been created to verify several

findings in more physiologically realistic models (yousra *et al.*,2013). The structure of the HCV virion remains poorly understood despite significant advancements in the production of viral particles in cell culture and numerous biochemical and morphological studies. The well-characterized flavivirus viral particles contrast with this (Manns *et al.*,2011). The interaction of the HCV virus with lipoproteins, which have an exceptionally low buoyant density, is a conspicuous and distinctive aspect of HCV biology (Fried *et al.*,2012). HCV particles range in size from 50 to 80 nm and contain the envelope glycoproteins E1 and E2, the single-stranded RNA genome, and the core (Pawlotsky,2014). In order to create the nucleocapsid, which is encased in a lipid membrane known as the viral envelope and to which the envelope glycoproteins are attached, the HCV genome interacts with the core protein. Significantly, Apo lipoproteins such as apo E, apo β , apoA1, apoC1, apoC2, and apoC3 can also be identified in conjunction with HCV particles because virion interaction with lipoproteins (Drexler *et al.*, 2013). Moreover, cholesteryl esters make up nearly half of the total lipids in cell culture-produced particles, whose lipid makeup is similar to that of very-low density lipoproteins (VLDL) and low-density lipoproteins (LDL). The pleomorphic nature of HCV particles is confirmed by electron microscopy examinations of purified infectious virions, which also reveal virions with a rather even and smooth surface (Ouane *et al.*,2013). The precise nature of the interactions between the lipoproteins and the HCV virion components is still unknown. According to certain theories, the HCV virion could be a hybrid particle made up of both a lipoprotein and a virion moiety. (Simmonds, 2013). Other theories have been put forth, however, in which apolipoproteins interact with the lipids or proteins of the HCV envelope to proximally connect lipoproteins with conventional viral particles (Manns, 2016). The association with lipoproteins in both particle types may help protect HCV glycoproteins from the host immune response and explain why HCV glycoproteins are difficult to detect or are not readily available at the virion surface (Zein, 2010). It's significant that the Apo lipoprotein(s) linked to the HCV virion participate in HCV entrance. The most important HCV entry-determining viral components are HCV envelope glycoproteins. They do, in fact, participate in receptor binding and mediate the fusion of an endosomal host cell membrane with the viral envelope. Inside infected cells, the type 1 transmembrane proteins E1 and E2 of the HCV form a non-covalent heterodimer. whereas they form on the viral particle as massive covalent complexes stabilized by disulfide bonds. (Bukh,2012). It has been demonstrated that the E2 glycoprotein interacts with receptors or co-receptors on target cells when it forms the E1E2 heterodimer (Billerbeck *et al.*, 2013). E2 has also initially been postulated to be the fusion protein responsible for the fusion between the HCV envelope and a host-cell membrane on the grounds that the structure of the fusion protein should be conserved among the Flaviviridae family (Bartosh *et*

al.,2013). This theory, however, is not supported by recently published crystal structures of the E2 glycoprotein core domain (Lindenbachy, 2015). Additionally, E2 creates a compact globular structure that is different from any other viral fusion protein known to exist, as opposed to the previously predicted three-domain, elongated shape. It's interesting to note that the delineation of the CD81 binding site and the masking of neutralizing epitopes by glycans in this novel structure support earlier experimental findings (Zhong *et al.*,2015). These new findings also overwhelmingly support the idea that E1 ought to be the fusion protein or, at the very least, a fusion partner of an E1E2 fusion complex produced by conformational rearrangements (Lagaya *et al.*,2012).

6.1.2. Clinical Picture of HCV

6.1.2.1 Acute infection

Hepatitis C infection causes acute symptoms in 15%of case (Tong *et al.*,2005). Rarely does severe liver failure occur; instead, symptoms are typically moderate and nebulous and include decreased appetite, weariness, nausea, discomfort in the muscles or joints, and weight loss. Jaundice is not usually present in situations of acute infection. In 10–50% of cases, the illness goes away on its own; this happens more frequently in young, female people. (Cavlek *et al.*,2009).

6.1.2.2 Chronic infection

About 80% of those exposed to the virus develop a chronic infection. The presence of detectable viral replication for at least six months is what is meant by this. In the first few decades after contracting the virus, the majority of people show little to no symptoms. Persistent hepatitis C might cause modest cognitive issues and weariness (Gamage *et al.*,2011). After several years, a chronic infection may result in cirrhosis or liver cancer. 7-53% of people have normal liver enzymes. There have been reports of late relapses following apparent cures, although it can be challenging to tell them apart from reinfection (Haruna *et al.*,2011). About half of infected individuals get fatty liver abnormalities, which are often present before cirrhosis develops. (Ortiz *et al.*,2012). Cirrhosis is more common in those also infected with hepatitis B, Schistosoma, or HIV, in alcoholic and in those of male gender. In those with hepatitis C, excess alcohol increases the risk of developing cirrhosis 100-fold (Belec *et al.*,2013). Liver cirrhosis can cause jaundice, varices (enlarged veins, especially in the stomach and esophagus), ascites (accumulation of fluid in the abdomen), easy bruising or bleeding, portal hypertension, ascites, ascites, ascites, ascites, and a syndrome of cognitive impairment known as hepatic encephalopathy. More than half of those with a persistent infection develop ascites at some point. (Figueiredo *et al.*,2014).

6.2 Viral Hepatitis Type B (HBV)

The Hepatitis B virus (HBV) is a major public health concern around the world. More than 240 million people are hepatitis B surface antigen (HBsAg) positive chronic HBV (CHB) carriers, according to the World Health Organization (WHO), and are at risk of developing catastrophic liver illnesses such as cirrhosis and hepatocellular carcinoma. (HCC) (WHO.,2015). While testing sera from patients who had received numerous blood transfusions, Blumberg and Alter (1965) discovered that two of the sera from hemophilic patients had an Ag that was later dubbed the Australian antigen (Au), as the serum was from an Australian inherent population (currently called as HBsAg). The HBsAg was found in many hepatitis patients' serums, according to Prince (1968) then Dane and Cameron (1970) identified the viral particles in sera from patients with positive (Au) via electron microscopy. Galibert *et al.* (1979) (later in the 1970s) discovered the HBV genome's nucleotide (nt) sequence. Hepatitis B virus belongs to the hepadnaviridae family, which includes a collection of highly species specific DNA HBV (Inan and Tabak, 2015). Hepadnaviruses display a high preference to infect liver cells and a tight host range specificity, so that HBV only infects humans. Animal hepadnaviruses are the only causative agents for the regarding animal hosts (Schulze *et al.*, 2012). Hepatitis B is a leading cause of liver illness, and it can lead to both acute and chronic liver inflammation (Schadlar and Hildt, 2009). Subclinical (asymptomatic) infection or mild disease might progress to severe or even fulminant hepatitis (WHO, 2015). Hepatitis B can lead to long-term complications such as chronic hepatitis, cirrhosis, and liver cell cancer, making it one of the world's most serious health problems (Zhang *et al.*, 2013; Inan and Tabak, 2015). It's an enveloped DNA virus from the Hepadnaviridae family (Table 1-4) and the Orthohepadnavirus genus (hepadnavirus=hepatitis DNA virus" (WHO, 2015).

Hepadnaviridae is divided into two genera. Orthohepadnavirus is a genus of mammalian viruses. Viruses that are identical to human HBV have been found in a variety of primates (chimpanzees, gorillas, ground squirrels, orang-utans and gibbons). HBV varieties that infect birds (herons, storks, and ducks) are known as avihepadnaviruses (Schaefer, 2007). The hepatitis B virus is a pathogen that has double-stranded DNA. To distinguish HBV from other hepatitis-causing viruses with an RNA genome, the term "hepadnaviruses" was coined, which stands for "hepatitis DNA viruses" (Schaefer, 2007).

Table (4): The main characteristics of Hepadnaviruses (Carroll *et al.*, 2016)

Virion	overall diameter of 42 nm (nucleocapsids, 18 nm)
Genome	3.2 kbp of circular, double-stranded DNA in one molecule. Positive DNA strand is only partially complete in a virion, while the negative DNA strand is fully developed. At the start of the replication cycle, the gap must be filled.

Proteins	HBsAg contains two main polypeptides, one of which is glycosylated, while HBcAg only contains one.
Envelope	contains lipid and HBsAg
Replication	with the help of the DNA genome's middle RNA copy (HBcAg in nucleus; HBsAg in cytoplasm). Both the mature virus and 22-nm spherical particles are made of the HBsAg discharged from the cell surface.
Outstanding characteristics	The family contains a wide variety of different species that can infect both humans and other animals (eg, woodchucks, squirrels, ducks). produce both acute and chronic hepatitis, which frequently progresses to liver cancer and lifetime carrier status.

Hepatitis B virion is a mature, spherical virion known as a "Dane particle." It is a 42 nanometer diameter double shelled sphere. The external envelope shell, which is 7 nm thick and detergent-sensitive, is made up of three glycoproteins: surface (S), preS1 and preS2 proteins (HBsAg), and the internal core unit is the viral nucleocapsid, which includes polymerase and the viral genome (DNA) (Bruss., 2004). The spherical capsid demonstrates icosahedral symmetry and comprises 180 capsomers (HBc antigen) with a diameter of 30 to 35 nm and There are two further subviral components in addition to the mature virion: the spherical form (22 nm in diameter) and the filamentous shape (22 nm in diameter with different lengths of 50 to 230 nm) (Figure 1.1a and b). These molecules are usually non-infectious forms of HBV (HBsAg) that lack the core components yet can be

found in HBV carriers' serum. The Dane unit is thought to be the source of HBV infection (Gerlich, 2013). The transcription of viral structural proteins in the negative strand involves many different proteins, including those involved in viral replication such as surface, core, pre-S, and e proteins as well as X and polymerase proteins. Four open reading frames (ORFs) encoding seven polypeptides, DNA polymerase, a small trans activator transcriptional and big polymerase protein with RNase H activity, and reverse transcriptase were all discovered. The S gene contains polypeptides containing pre-S1 and pre-S2 sequences in addition to three frame beginning codons that encode significant HBsAg. The HBcAg and HBe proteins are created when the gene C's two in-frame beginning codons are joined to create the soluble HB e antigen. (Carroll *et al.*, 2016).

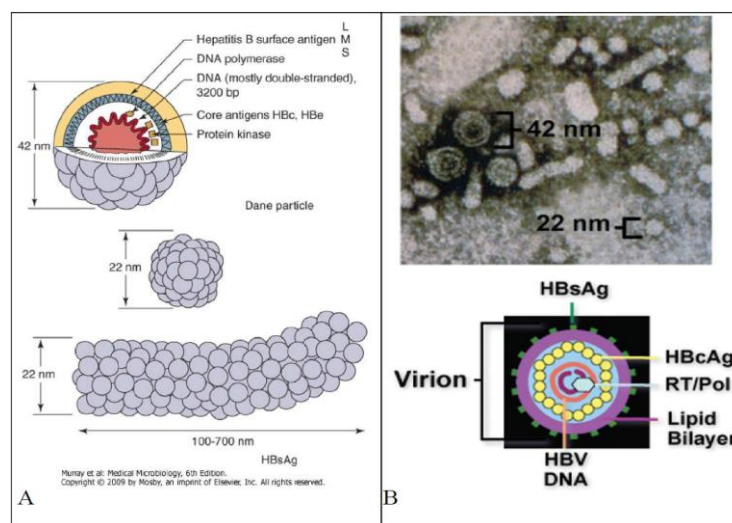


Figure (2) A: Schematic drawing of HBV particles and the two HBsAg subviral particles. B: Electron micrograph of circulating forms of HBV particles in the blood (top) and Dane particle the infectious HBV particle (bottom) (Murray *et al.*, 2009).

Across the world, the hepatitis B virus (HBV) is a serious public health issue (WHO,2015). With the exception of those who are immunocompromised, 95% of adult hepatitis B patients recover with little to no therapeutic treatment, despite the fact that HBV poses a serious health risk to more than two billion people, or one-third of the world's population. (WHO,2019). Hepatocellular carcinoma and liver cirrhosis can be brought on by HBV (Mehta and Reddivari ,2021). Hepatitis B virus infection especially chronic infection is

a public health challenge on the same grade as HIV, tuberculosis, and malaria (Revill *et al.*, 2019). By coming into touch with contaminated blood or other bodily fluids through mucosal membranes or non-intact skin Hepatitis B virus (HBV) is transmitted. The majority of new infections are symptomless. Acute liver failure is uncommon in infants and children, although it occurs in 0.5 % to 1.0 % of adult cases, with a 20 % to 33 % case fatality rate. Chronic hepatitis B is found in more than 80% of prenatal infections, but only 5% of healthy

individuals are affected. The clinical severity of chronic hepatitis B infection ranges from asymptomatic to liver cirrhosis and hepatocellular cancer (WHO.,2017). The identification of serum HBV markers is commonly used to make a hepatitis B diagnosis. According to several research, an increase in blood leptin levels in HBV infection is related to inflammatory cytokines, adipose tissues, and macrophage phagocytosis. Leptin-induced macrophage production of inflammatory cytokines such TNF-, IL-6, and IL-12 may exacerbate liver necrosis and degeneration. Leptin, which is generated in a number of organs including the liver, is crucial for hepatic fibrogenesis and inflammation in viral liver diseases. Lipid peroxidation and pro-inflammatory reactions are also possible effects of leptin (Şenol and Toraman,2021; Hala,2022). Patients with a variety of acute and chronic disorders can easily have their glucose metabolism changed, leading to hypoglycemia, impaired glucose tolerance (IGT), or diabetes (Hamed *et al.*, 2019). The two enzymes with the greatest clinical importance in viral hepatitis and other types of liver illness linked to hepatic necrosis serum have been indicated to be AST, and ALT. levels of AST and ALT, which are increased even before the clinical symptoms of illness (as jaundice) manifest. The highest limits of the reference range may be reached by both enzyme levels (Hala,2022). Nitric oxide (NO) and its byproducts have a substantial impact on the physiology and pathophysiology of the liver. Despite its numerous and complex functions, nitric oxide has been shown to have specific patterns of influence on the etiology and development of liver illnesses (Iwakiri and Kim,2015). SOD (superoxide dismutase) is an essential part of the antioxidant defense mechanism. SOD is the first and most crucial line of enzymatic defense against oxidative stress, especially oxygen free radicals, among the antioxidant defense mechanisms (Zhang, *et al.*, 2016). Cytokines are crucial for the progression of viral hepatitis infections. Different immune cells can produce cytokines, which have the ability to destroy viruses by inducing an immunological response. (Nihayet and Mehmet,2020) . IL-6 is a multipurpose cytokine that is essential for inflammation, cell differentiation, and tumor growth. In order to activate the classical or trans signaling cascades, IL-6 can bind to soluble or membrane-bound IL-6 receptors (IL-6R), respectively (Okamoto *et al.*,2010; Hala,2022). IL-33 is a multifunctional cytokine that plays a role in a number of medical diseases (Mok *et al.*, 2010). IL-33 can activate the MAP-kinase and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathways via the ST2 and IL-1RaP receptor complex, boosting the production of cytokines and the Th2 response (Schmitz *et al.*, 2005).The TGF-III protein, which is particularly prevalent in tissues that develop into skeletal muscles, is crucial for the growth of these muscles, the protein also has a role in the development of blood vessels, regulation of bone growth, healing of wounds, and immune system activity, to effect its activities, TGF-III interacts to receptor proteins TGF-IIIR

on cell surfaces ,this binding starts the transmission of signals inside the cell, enabling the regulation of a variety of cellular activities (Bertoli *et al.*, 2015).

VII. REPLICATION OF HBV

Because HBV replicates through reverse transcription of an intermediate RNA, like retroviruses, its replication cycle is complex and unique. The attachment and entry of mature virions into host hepatocytes through the cell membrane's sodium taurocholate co-transporting polypeptide (NTCP) receptor is the initial stage of HBV replication. (Yan.,2012). In the nucleus, the host and viral polymerase repair the nucleocapsid to produce a covalently closed circular DNA after it is released from the viral envelope in the cytoplasm (ccc DNA). All viral RNAs, including the pre genomic RNA, are transcriptionally transcribed using the ccc DNA, which creates a micro chromosome (pgRNA, a 3.5 kb RNA intermediate that serves as a translation template for HBV core and polymerase proteins as well as a template for reverse transcription to viral DNA) (Mauss *et al.*,2017). The transcripts are then translated into viral proteins in the cytoplasm after being exported there. The core proteins assemble into immature RNA-containing nucleocapsids when RT binds to pg RNA in the cytoplasm. After that, pgRNA is reverse transcribed by RT to create the viral rc DNA genome, maturing the immature nucleocapsids. To replenish the ccc DNA pool, nucleocapsids are either imported back into the nucleus or they are enclosed and discharged as mature virions (Locarnini and Zoulim.,2010). Figure (3) depicts a schematic representation of the HBV replication cycle.

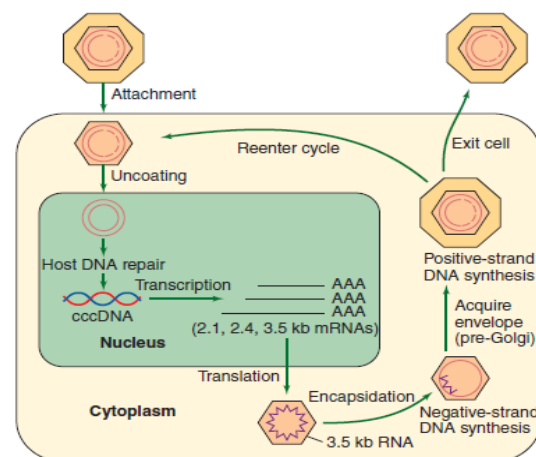


Figure: (3) HBV replication cycle (Carroll *et al.*, 2016).

VIII. EPIDEMIOLOGY OF HBV

8.1. Sources and Transmission Methods

Hepatitis B virus can be discovered in a variety of body fluids, including saliva, blood, sperm, menstrual blood, vaginal secretions, breast milk, perspiration, urine

from chronically or acutely infected patients, and tears. Hepatitis B virus can survive in the environment for seven days or more at room temperature, and it is easily spread by contact with contaminated bodily fluids. It is 100 times more infectious than HIV and 10 times more infectious than HCV (Daniel, 2004).

HBV is spread through coming into contact with an infected person's blood, sperm, or other bodily fluids. It can be passed on from mother to child at birth or during childhood. 80–90% of infants who have an infection in the first year of life do so chronically. Transmission can also happen through unprotected sex and the reuse of needles, syringes, and other medical equipment in health care settings or among drug users. Hepatitis B can be transferred by medical and dental procedures, tattooing, piercing, sharing personal hygiene products, razors, and nail care supplies contaminated with infected blood. The danger of contracting hepatitis B is high for medical personnel. HBV cannot be transmitted through casual contact with an infected person, such as hugging, kissing, sharing meals or beverages, or through breastmilk, food, or water. (WHO.,2019).

8.2 vaccination

In 1981, the US government approved the first hepatitis B vaccination. In 1986, a recombinant version was released (Who.,2017). And it is both (Recombivax HB, Engerix-B, Heplisav-B) safe and effective. It is now used in many nations in early childhood in the general population (Niederau.,2014). The recombinant vaccination is based on the Hepatitis B surface antigen (HBsAg) gene, which has been put into yeast (*Saccharomyces cerevisiae*) or cells that are free of any worries about human blood products. (Tulchinsky and Theodore.,2018). As a result, the yeast can manufacture only the noninfectious surface protein, with no risk of transferring genuine viral DNA into the final product (Offit and Paul.,2007). This is the vaccination that is currently in use. It is on the World Health Organization's List of Essential Medicines (WHO.,2019). Both versions were developed by Maurice Hilleman and his team (Tulchinsky and Theodore,2018).

The first dose should be given within 24 hours of birth, followed by two or three subsequent doses (WHO,2017). This includes those with poor immune function such as from HIV/AIDS and those born premature. Also Vaccination of health-care personnel is also suggested. In healthy people, routine immunization protects more than 95 percent of the population (Chen.,2005). In people who are at high risk, blood testing to ensure that the immunization has worked is recommended. Additional doses may be required in persons with weakened immune systems, but they are not required in the majority of cases. Hepatitis B immune globulin should be provided in addition to the vaccine to persons who have been exposed to the hepatitis B virus (HBV) but have not been inoculated. The vaccine is administered through a muscle injection (WHO,2017). The hepatitis B vaccine has extremely few serious side

effects. Pain may develop at the injection location. It's perfectly safe to use during pregnancy and breastfeeding. There is no evidence that it is associated to Guillain–Barré syndrome. Recombinant DNA techniques are used to create hepatitis B vaccinations. They can be purchased separately or in conjunction with other vaccines (WHO,2017).

8.3 Treatment

The major goals of chronic HBV treatment are to reduce liver inflammation, prevent liver cirrhosis and failure, and reduce the risk of HCC by inhibiting HBV replication (Aspinall *et al.*, 2011). Treatments for hepatitis B are one of the necessary preventative steps that should be monitored while developing viral hepatitis control and prevention programs (Daniel, 2008). Antiviral medications can last a lifetime, and in some situations, they can reduce a patient's infectivity while also improving their quality of life. (Benjamin and Margaret, 2011). Despite the fact that none of the medications on the market can treat the infection, they can prevent the virus from multiplying, lessening the liver's damage. As of 2018, there are eight drugs in the US that are authorized to treat hepatitis B infection. These include immune system modulators like interferon alpha-2a and PEGylated interferon alpha-2a as well as antiviral medications like lamivudine, adefovir, tenofovir disoproxil, tenofovir alafenamide, telbivudine, and entecavir. The World Health Organization recommended tenofovir or entecavir as first-line medications in 2015. (WHO,2017).

IX. WORLDWIDE PREVALENCE OF HCV

Hepatitis C is found worldwide, the most affected region are Eastern Mediterranean and European regions, with the prevalence of 2.3% and 1.5% respectively (WHO,2017). The considerable genetic diversity of the hepatitis C virus (HCV) is reflected in geographical differences in genotype prevalence. This presents a problem for the advancement of pan-genotypic therapies and vaccines, which depend on taking worldwide trends in HCV genotype prevalence into account (Timm *et al.*,2007). The seven genotypes (1-7) that have been found for HCV strains based on phylogenetic analysis and sequencing of the entire viral genomes are mutually exclusive. Several genotypes of HCV strains differ at 30–35% of the nucleotide locations. HCV is further divided into 67 confirmed and 20 speculative subtypes within each genotype. Around 15% of nucleotide locations are different between strains of the same subtype (Smith *et al.*,2014). The regional distribution of HCV genotypes today is complicated. It has already been proven that a small number of subtypes, notably 1a, 1b, 2a, and 3a, are globally prevalent and are responsible for a significant portion of HCV infections in high income nations. Prior to the identification of HCV, these so-called epidemic subtypes are believed to have

spread quickly through the use of contaminated blood and blood products, injecting drug use, and other vectors (Magiorkinis *et al.*,2009). Many additional HCV subtypes are regarded as endemic strains; they are very uncommon and have persisted for a long time in more constrained areas. Endangered strains of genotypes 1 and 2 are mostly found in west Africa, south Asia, central and eastern Africa, southern Africa, and east Asia. Only one genotype 7 infection has ever been documented as of 2015, and it was identified in Canada from an immigrant from central Africa (Jane *et al.*,2015). Historical and current trends in human migration have probably had an impact on the global distribution of HCV genetic diversity. For instance, it appears that the trans-Atlantic slave trade allowed the spread of strains from west Africa to the Americas. (Markov *et al.*,2012). In wealthy nations, the frequency of HCV infection ranges from 0.2-2.2%, while it is around 7% in developing nations. The two main methods of transmission were blood transfusions (18.14%) and surgery (8.94%). Ages 50 to 59 had the highest frequency of HCV infection (25 to 85%) (Hajarizadeh *et al.*,2013). Until the age of 60, female patients had considerably greater rates of HCV prevalence than male patients, whereas the inverse was true after that age. The most prevalent HCV genotype was subtype 1b, followed by 2a, and it was more prevalent in female patients than in male ones (Hanafiah *et al.*,2013). For both male (73.27%) and female (73.47%) patients, genotype 1 had the highest prevalence of all genotypes, followed by genotype 2. Three genotypes—genotype 1 (male: 29.84% versus female: 43.55%, genotype 2 (male: 6.25% versus female: 10.89%, and genotype 6 (male: 1.41% versus female: 1.81%) were more prevalent in female patients than in male patients, whereas genotype 6 showed no discernible gender differences (Zhili *et al.*,2016). Egypt reportedly has the highest recorded frequency of this virus worldwide (Jane *et al.*,2015). According to the research done, the prevalence of HCV in the general population varied, ranging from 13 to 22% in each case. The frequency of HCV was reported to be 14.5% among blood donors, 7.7% among healthcare professionals, 12.1% among rural primary school students, 18.1% among residents of rural communities, and 22.1% among army recruits. It was shown that the most prevalent HCV genotype in Egyptians was genotype 4, specifically subtype 4a. Recent research, however, has shown the presence of additional genotypes and subtypes, such as 1a, 1b, and 2a, demonstrating the tremendous variability of HCV genotypes (Selm,2010). Using a large, nationally representative sample, the Egyptian Demographic Health Survey (EDHS), a cross-sectional survey that included a hepatitis C virus (HCV) biomarker, was undertaken in 2008. It projected that 14.7% of people in the 15- to 59-year-old age group had the virus (Alnaqdy *et al.*,2013). As a result, Egypt has the highest global HCV prevalence rate. HCV infection and its sequelae are currently among Egypt's most pressing public health issues (Mudawi,2008).

9.1. Prevalence of HBV

The Hepatitis B virus is most prevalent in African and Asian countries, where the carrier rate surpasses 8% (range 8-15%), with a lifetime infection risk of 60%. The virus spreads predominantly through vertical transmission and child-to-child encounters in these areas. Transmission of the virus occurs predominantly through sexual intercourse and intravenous drug use in places with lower incidence, such as North America, where the carrier rate is under 2%, with a lifetime chance of infection of 2% (Hamborsky *et al.*,2015). Sub-Saharan Africa (> 75 million, prevalence estimate 8.83%) and the Western Pacific region (> 95 million, prevalence estimate 5.26%) account for the majority of chronic carriers and 70% of the global HBV burden. (Schweitzer *et al.*,2015). HBV has now infected over 2 billion individuals worldwide, with over 360 million becoming chronically infected (infections lasting greater than 6 months). Despite the fact that a vaccination with a 95% efficiency was launched in the late 1980s, each year about 4.5 million people become sick around the world. 90% of newborns infected before the age of one will develop chronic infections, but the likelihood of chronic infection declines to between 30% and 50% for those infected between the ages of one and four. HBV-related liver cancer or cirrhosis (severe scarring/loss of functional liver tissue) kills about a quarter of those chronically infected in these age groups (Franco *et al.*,2012). Is high for medical personnel. No breastfeeding, food, water, or casual contact with an infected person (such as a hug, kiss, or sharing of food or drinks) is permitted. (WHO.,2019).

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