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Epidemiological Study and Prognostic Value of Some Biochemical, Hematological and Oxidative Stress Markers to Follow up and Prevent Complications of Hepatitis B in Patients of EL-Oued Region

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You are the teacher who succeeded in inspiring us, in giving us confidence in ourselves and in the future, but also in making us want to learn. Thank you for everything you have done for us!!

A teacher like you we would never forget!

to our supervisor ***Dr. DEROUICHE Samir.***

الإهداء

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ولقول الامام الشافعي طيّب الله ثراه :

"اصبر على مرّ الجفا من معلمٍ فإنَّ رسوبَ العلمِ في نفراتهِ..... ومنْ لم يذق مرَّ التعلمِ ساعةً تجرَّعَ نلَّ الجهل طولَ حياته

ومن فاتهُ التَّعليمُ وقتَ شبابهِ فكبِّر عليه أربعاً لوفاته..... وَذَاتُ الْفَتَى - واللهِ - بالْعِلْمِ وَالتُّقَى إذا لم يكونا لا اعتبار لذات"

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Abstract

Viral hepatitis is one of the most important liver diseases and is a viral infection that affects the liver and can cause acute and chronic diseases. The aim of our work is carried out an epidemiological study and evaluation of biological and oxidative stress markers in patients with hepatitis B in El-Oued region. Our epidemiological study was carried out on hepatitis patients admitted to Ben Omar Djilani hospital in the period between January 2013 to December 2020 in Wilaya of El-Oued. Our biological markers study was conducted on 30 voluntary divided into healthy (controls) and patients group, they were used to study the hematological , Biochemical and oxidative stress markers, for screening and follow-up hepatitis.

The results of the epidemiological study showed that 1798 cases of hepatitis infection were registered. 72.14% of them were aged between 20 to 40 years. On the other hand, 57.30 % of hepatitis patients are men versus 42.70% are women. In this study, 95% of the patients were infected with hepatitis B whereas 5% were infected with hepatitis C. Concerning the distribution of hepatitis, the eastern and central region include the highest numbers of patients with 37% and 33% respectively. For the biological study, our results revealed a significant change ($p< 0,05$) of some hematological , biochemical and oxidative stress markers in hepatitis B patients as compared to controls. From this study we found that some of oxidative stress markers have a high sensitivity, specificity and AUC values which qualify them to be important marker for follow up and predicting complication of hepatitis B. On one hand this study showed a significant ($p<0,05$) relationship between the changes of some specifics oxidative stress markers with some hematological and biochemical markers.

In conclusion, the change in hematological , biochemical and their relationship with oxidative stress contributes to the development or complication of the disease after hepatitis. Suggesting that MDA, GSH, CAT, SOD and ORAC testing used as systemic marker for screening and followed hepatitis B treatment.

Key Words: Hepatitis B, Hepatitis C, Liver, Epidemiology, Oxidative stress, El Oued.

الملخص

مرض التهاب الكبد الفيروسي يعتبر من اهم امراض الكبد فهو عدوى فيروسية تصيب الكبد ويمكن أن تسبب أمراضا حادة ومزمنة. الهدف من عملنا هو اجراء دراسة وبائية وتقييم بعض العوامل البيولوجية ومعايير الاجهاد التأكسدي لدى مرضى الالتهاب الكبد الفيروسي توع ب في منطقة الوادي. أجريت دراستنا الوبائية على المصابين بالتهاب الكبد الفيروسي ب الذين تم تشخيصهم في مستشفى بن عمر الجيلاني في الفترة الممتدة من جانفي 2013 إلى ديسمبر 2020 بولاية الوادي. اما الدراسة البيولوجية فقد أجريت على 30 شخص مقسمون إلى مجموعة من الأصحاء (شواهد) ومجموعة اخرى مصابة بالمرض وهذا من اجل تقييم تغيرات بعض المؤشرات البيولوجية (مكونات الدم، العوامل البيوكيميائية وعوامل الإجهاد التأكسدي) وذلك لفحص ومتابعة مرض التهاب الكبد الفيروسي ب.

أظهرت نتائج الدراسة الوبائية أن 1798 حالة التهاب كبد ب تم تسجيلها, من بينهم 72,14 % تتراوح أعمارهم من 20 إلى 40 سنة. من ناحية أخرى، فإن 57,30 % من مرضى التهاب الكبد هم من الرجال مقابل 42,70 % من النساء. في هذه الدراسة أصيب 95 % بالتهاب الكبد ب بينما أصيب 5 % بالتهاب الكبد س. فيما يخص توزيع التهاب الكبد عبر الولاية فقد ضمت المنطقتين الشرقية والوسطى أعلى نسبة من المرضى بنسبة 37٪ و 33٪ على التوالي. فيما يتعلق بالدراسة البيولوجية، كشفت نتائجنا عن تغير كبير ($P <0,05$) في بعض مكونات الدم و المعايير البيوكيميائية و مؤشرات الإجهاد التأكسدي في مرضى التهاب الكبد ب مقارنة بالشواهد. في هذه الدراسة وجدنا أن بعض مؤشرات الإجهاد التأكسدي لديهم حساسية ونوعية وقيم AUC عالية تؤهلهم ليصبحوا مؤشرات مهمة للتشخيص والتنبؤ بالتهاب الكبد ب. من جهة أظهرت هذه الدراسة وجود ارتباط معنوي ($P <0,05$) بين تغير بعض مؤشرات الإجهاد التأكسدي مع إحدى مكونات الدم و المعايير البيوكيميائية .

في الختام، تساهم دراسة التغير في مكونات الدم و المعايير البيوكيميائية وعلاقتها بالإجهاد التأكسدي في تطور المرض أو مضاعفاته بعد الإصابة بالتهاب الكبد ب حيث نقترح استعمال وادراج معايير MDA, SOD, GSH, CAT, ORAC ضمن المؤشرات البيولوجية للمساهمة في الكشف، فحص ومتابعة التهاب الكبد ب.

كلمات مفتاحية: التهاب الكبد ب، التهاب الكبد س, الكبد, دراسة وبائية, اجهاد تأكسدي, الوادي.

Abbreviation list

AFL: alcoholic fatty liver.

AFP: Alpha-fetoprotein.

AIH: Autoimmune hepatitis.

ALD: Alcoholic liver disease.

ALF: Acute liver failure.

ALP : Alkaline phosphatase.

ALT: Alanine Aminotransferase.

ARE: Antioxidant Response Elements.

ASH: alcoholic steatohepatitis.

AST: Aspartate Aminotranferase.

ATP: Adenosine Triphosphate.

AUD: alcohol use disorder.

BHT: Butylated hydroxytoluene.

Br_3^-: Brom.

CAT : Catalase.

CD8: Cluster Differenciation 8.

CHB: chronic hepatitis B infection.

CHD: coronary heart disease.

$CI_{95\%}$: Asymptotic 95% Confidence Interval.

Cl^-: Chlore.

CRP : C-reactive protein.

CuSO 4: Copper Sulfate.

CuZn-SOD: copper-zinc SOD.

DNA: Deoxyribonucleic Acid.

DTNB :5,5′-Dithiobis (2-nitrobenzoic acid).

ECM: extracellular matrix.

ECSOD: extracellular SOD.

EDTA: Ethylene di-amine tetra-acetic acid.

ELAM : Endothelial Leucocyte Adhesion Molecule.

Fe^{+}: Fer.

GBD: Global Burden of Disease.

GPx : glutathione peroxidase.

GPX: Glutathion Peroxydase.

GR : glutathione reductase.

GSH: Reduced Glutathione.

GSS: glutathione synthetase.

GSSG: oxidized glutathione.

H2O2 : Hydrogen Peroxyde.

HAV: Hepatitis A Virus.

HBsAg: Hepatitis B Surface Antigen.

HBV: Hepatitis B Virus.

HC: healthy control.

HCC: hepatocellular carcinoma.

HCL: Hydrochloricacid.

HCV: Hepatitis C Virus.

HDV: Hepatitis D Virus.

HEV: Hepatitis E Virus.

HGB : Hemoglobin.

HGV: Hepatitis G Virus.

HIV: Human Immunodeficiency Virus.

$HO2^-$: Hydroperoxyl.

HOBr : Hypobrromus.

$HOCl^{-:}$ Hypochlorous acid.

HOCL: Hyochlorus Acid.

ICAM: Intercellular Adhesion Molecule.

IFN- γ: Interferon Gamma.

IgG : Immunoglobulins G.

IgM : Immunoglobulins M.

IL-2 : Interleukin 2.

IL-4 : Interleukin 4.

IL-6 : Interleukin 6.

iNOS: inducible nitric oxide synthase.

IR : insulin resistance.

JNK: c-Jun N-terminal kinase.

KH_2PO 4, K_2HPO 4: Phosphate-buffered.

LPS: lipopolysaccharide.

LYM : Lymphocytes.

MDA : Malondialdehyde.

MnSOD: manganese SOD.

MPV : Mean Platelet Volume

NAC: N-acetyl cysteine.

NaCl: Sodium chloride.

NADPH: Nicotinamide adenine dinucleotide.

NAFLD: Nonalcoholic fatty liver disease.

NASH : Non-alcoholic steatohepatitis.

NBT: Nitroblue tetrazolium.

NEUT: Neutrophil.

NF-B: Nuclear factor binding

NF-B: nuclear factor binding.

NFKβ : nuclear factor kapa beta .

NFS: Numeration Formule Sanguine.

NO: Nitric Oxide.

Nrf2: NF-E2-related factor 2.

O2 ^{1}: Singlet oxygen.

O_2^- : Superoxide.

O2: Molecular oxygen.

O3: Ozone.

OH^{-}: Hydroxyl.

OLT: Orthotopic liver transplantation.

$ONOO^{-}$: Peroxynitrite.

ONOO・ : peroxynitrite .

OR: Odds Ratio.

ORAC: Oxygen Radical Absorbance Capacity.

OS: Oxidative stress.

OS: oxidative stress.

P: P Values.

P450: Cytochrome

PBC: Primary biliary cirrhosis.

PLT : Platelets

R_2: Person correlation.

RBC: Red blood cell.

RNA: Ribonucleic Acid.

RNS: Reactive Nitrogen Specie.

RO^{-} : Alkoxyl.

RO_2^{-} : Peroxyl.

ROM : reactive oxygen metabolites.

ROS: Reactive Oxygen Species.

SOD: Superoxide Dismutase.

TBA: Thiobarbituric acid.

TCA: Trichloroacetic acid.

TGF- ß: Transforming growth Factors ß.

TNFα : Tumor Necrosis Factor.

UA: Uric Acid.

USA: Uniter States America.

UV: Ultraviolet.

VCAM: Circulating Vascular Cell Adhesion.

WBC: White Blood Cell.

WHO: World Health Organization.

XD: Xanthine Dehydrogenase.

XOR: Xanthine Oxidoreductase.

α-IFN: Interferon alpha.

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Introduction

Introduction

The notion of viral disease dates back to the end of the nineteenth century, with the identification of diseases transmissible by ultra-filterable and invisible agents in electron microscopy. Viruses, initially defined by their size, are found in all animal species, in plants (including algae and fungi), in bacteria (bacteriophages).

Between the years 1940-1955, Five hepatotropic viruses were discovered as the main causes of viral hepatitis in the world: hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus and hepatitis E virus (Hubert, 2016). The prevalence of acute and chronic viral hepatitis A and E shows distinct geographic differences. (Hubert, 2016).

HBV infection is a serious global public health problem with approximately 250 million people chronically infected It is responsible for 500,000 to 1.2 million deaths per year and the cause of death worldwide. The prevalence of HBV infection varies considerably among geographic and population subgroups. (Ganem et al., 2004).

From 1990 to 2005, the prevalence of chronic HBV infection declined in most areas. This was most evident in central sub-Saharan Africa, tropical and central Latin America, Southeast Asia and central Europe. Despite the decrease in prevalence, the absolute number of HBsAg-positive individuals fell from 223 million in 1990 to 240 million in 2005. The decline in the prevalence of HBV infection may at least in part be related to expanded vaccination, suggested by the largest decline observed in Southeast Asian children (Ott et al., 2012).

- In 2015, the WHO estimated that 257 million people were living with chronic hepatitis B. That same year, hepatitis B had caused, according to the estimated 887,000 deaths, primarily from cirrhosis or hepatocellular carcinoma (i.e., primary liver cancer). (World Health Organization, 2017).
- In 2016, 27 million people (10.5% of the estimated total population of people living with hepatitis B) were aware of their infection, while 4.5 million (16.7%) of those diagnosed were under treatment. According to the latest WHO estimates, the proportion of children under 5 with chronic HBV infection fell to just under 1% in 2019 from around 5% in the pre-vaccination era.

The hepatitis B virus can survive outside the body for at least 7 days. During this time, it can still cause infection if it gets into the body of a person not protected by the vaccine. This virus has an incubation period which is 75 days on average, but can vary from 30 to 180 days. It can be detected within 30 days to 60 days of infection and persist in the body leading to chronic hepatitis B. (World Health Organization (WHO), 2017).

In viral hepatitis, cellular damage is predominantly determined by the immune response and, although the pathophysiology is very complex, there are a very large number of data demonstrating that the persistence of infection, the progression of liver damage and carcinogenesis are all steps in which oxidative-mediated pathways are involved. (Rizzetto et al., 1997)

Oxidative stress is an abnormal condition caused by an excess production of oxidants compared to the antioxidant (Samir et al., 2021 ; Nour El-Houda et al., 2020).

Many of recent landmarks in scientific research have shown that in human beings, oxidative stress has been implicated in the progression of major health problems by inactivating the metabolic enzymes and damaging important cellular components (Samir & Anfal, 2017) it is as a consequence of increase a reactive oxygen species and decrease in antioxidant defenses in prevalent in many health problems (Tan et al,.200). Reactive oxygen and nitrogen species (ROS, RNS) play a crucial role in the induction and in the progression of liver disease, independently from its etiology. They are involved in the transcription and activation of a large series of cytokines and growth factors that, in turn, can contribute to further production of ROS and RNS. The main sources of free radicals are represented by hepatocyte mitochondria and cytochrome P450 enzymes, by endotoxin-activated macrophages (Kupffer cells), and by neutrophils.

The first part: is an epidemiological study of hepatitis B in El-Oued region.

The second part: is an biological study concerns the determination of the variation and signification of some biochemical, hematological and oxidative stress markers in the prognostic and following up of hepatitis in patients from El-Oued region.

First part

Bibliographic part

I. General information on the liver

I.1. Liver anatomy

The liver is the largest internal organ in the body, accounting for approximately 2% to 3% of the total body weight of an adult (Skandalakis et al., 2004), which amounts to approximately 1400 g in females and 1800 g in males (Sibulesky, 2013) . It normally has a smooth surface contour and is tan-brown in color. (Kaplan et al., 2017)

The average transverse diameter is approximately 20 to 23 cm. The greatest measurement at the midpoint of the right lobe is 15 to 17 cm. The greatest anteroposterior diameter on a level with the upper pole of the right kidney is approximately 10 to 12.5 cm.

The liver assumes the shape of a pyramid or a wedge with the base directed to the right and the apex or thin leading edge toward the left (figure 01), thus presenting three major surfaces. A sharp, well defined margin is formed by the meeting of the superior and inferior surfaces, whereas the remaining margins are rounded.

The entire right hypochondrium is occupied by the liver which extends to the left across the midline where it comes into intimate relation with the anterior surface of the stomach, left kidney, and spleen. (Kennedy et al., 1977). It is enveloped by a fibrous membrane known as Glisson's capsule, The liver is also covered by visceral peritoneum anteriorly and posteriorly except for a bare area where it directly abuts the diaphragm. (Juza, 2014)

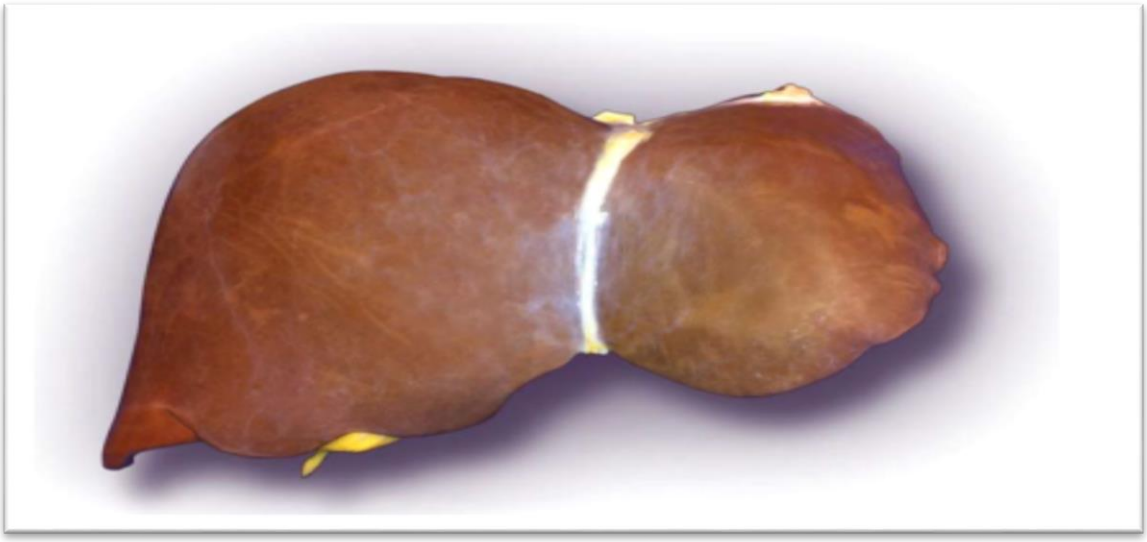


Figure 01: normal liver. (Sibulesky, 2013).

I.1.1. Peritoneal attachments (ligamentous)

Located in the right upper quadrant of the abdominal cavity beneath the right hemidiaphragm (figure 02), liver is protected by the rib cage (Abdel-Misih et al., 2010) and maintains its position through its attachment to the cava and parietal peritoneum on the abdominal cavity and the peritoneal folds or ligamentous attachments which continue as the Glisson's capsule over the surface of the liver. These ligaments are usually thin and avascular in the healthy state. Dividing these ligaments is the initial step in any major liver surgery or liver transplantation. (Reddy, 2018). Five attachments help to define hepatic segmentation and to separate the right and left livers (Lafortune et al., 2007).

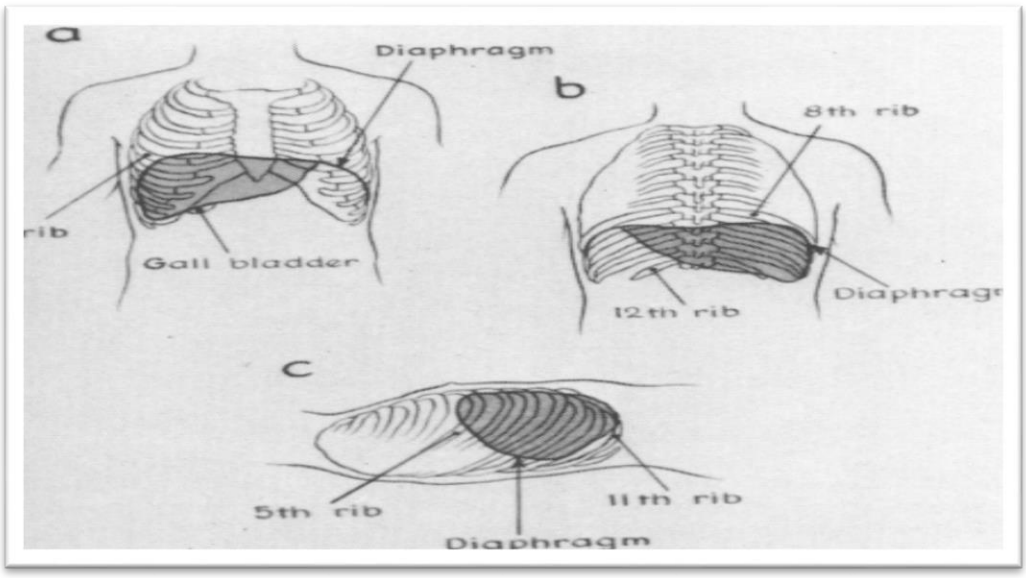


Figure 02: Skin surface projections of the liver; a, anteroposterior; b, posteroanterior; c, right lateral. (Kennedy et al., 1977).

I.1.1.1.Falciform ligament

The falciform ligament is made up of a fibrous ligament, within which there is a residue of the umbilical vein (Lafortune et al., 2007). It is an attachment arising at or near the umbilicus and continues onto the anterior aspect of the liver in continuity with the umbilical fissure. The falciform ligament courses cranially along the anterior surface of the liver, blending into the hepatic peritoneal covering (figure 03). (Abdel-Misih et al., 2010).

This ligament is very useful to recognize in radiological practice (Lafortune et al., 2007). The entrance of the obliterated umbilical vein along the free margin of the falciform ligament is commonly and erroneously used to distinguish the right from the left lobe. The falciform ligament in reality is a surface marking serving to delineate superiorly and anteriorly the junction of the medial and lateral segments of the left lobe of the liver. This line of division is well to the left of the plane separating the right and left lobes. (Kennedy et al., 1977).

I.1.1.2.Round ligament (ligamentum teres)

Within the lower edge of the falciform ligament is the ligamentum teres (round ligament) (figure 03), a remnant of the obliterated umbilical vein (ductus venosus) that travels from the umbilicus into the umbilical fissure. During fetal life, the ductus venosus is responsible for shunting a majority of blood flow of the umbilical vein directly into the IVC, transporting oxygenated blood from the placenta to the fetus. After birth, the umbilical vein closes as the physiologic neonatal circulation begins. In the presence of portal hypertension, the umbilical vein may recanalize to allow portasystemic collateralization through the abdominal wall, known as caput medusae. . (Abdel-Misih et al., 2010).

I.1.1.3.Coronary ligament

At the cranial aspect of the liver is a convex area along the diaphragmatic surface that is devoid of any ligamentous attachments or peritoneum “the bare area” (figure 03). The coronary ligament lies anterior and posterior to the bare area of the liver comprised of peritoneal reflections of the diaphragm. (Abdel-Misih et al., 2010).

The bare area lies between the anterior or upper layer of the coronary ligament and the posterior or lower layer in which the inferior vena cava and hepatic veins are located, it is attached to the diaphragm by flimsy fibroareolar tissue. (Kennedy, 1977)

I.1.1.4.Triangular ligaments

The extreme right and left of the liver, the two leaves of the coronary ligament join laterally to form the triangular ligaments (figure 03). (Kennedy, 1977).

The right coronary and right triangular ligaments course posterior and caudally toward the right kidney, attaching the liver to the retroperitoneum. (Abdel-Misih et al., 2010).

I.1.1.5. ligamentum venosum

The ligamentum venosum (figure 03) represents the remnants of the ductus venosus, which is established in the fetus to allow blood to return from the placenta to reach the heart without needing to pass through the sinusoids of the liver. It is a fibrous cord that passes from the left portal vein to the left hepatic vein just before it enters the inferior vena cava (Hur, M.-S., 2014). The ligamentum venosum lies within a fissure on the inferior surface of the liver between the caudate lobe posteriorly and the left lobe anteriorly, where it is also invested by the peritoneal folds of the lesser omentum (gastrohepatic ligament). (Abdel-Misih et al., 2010).

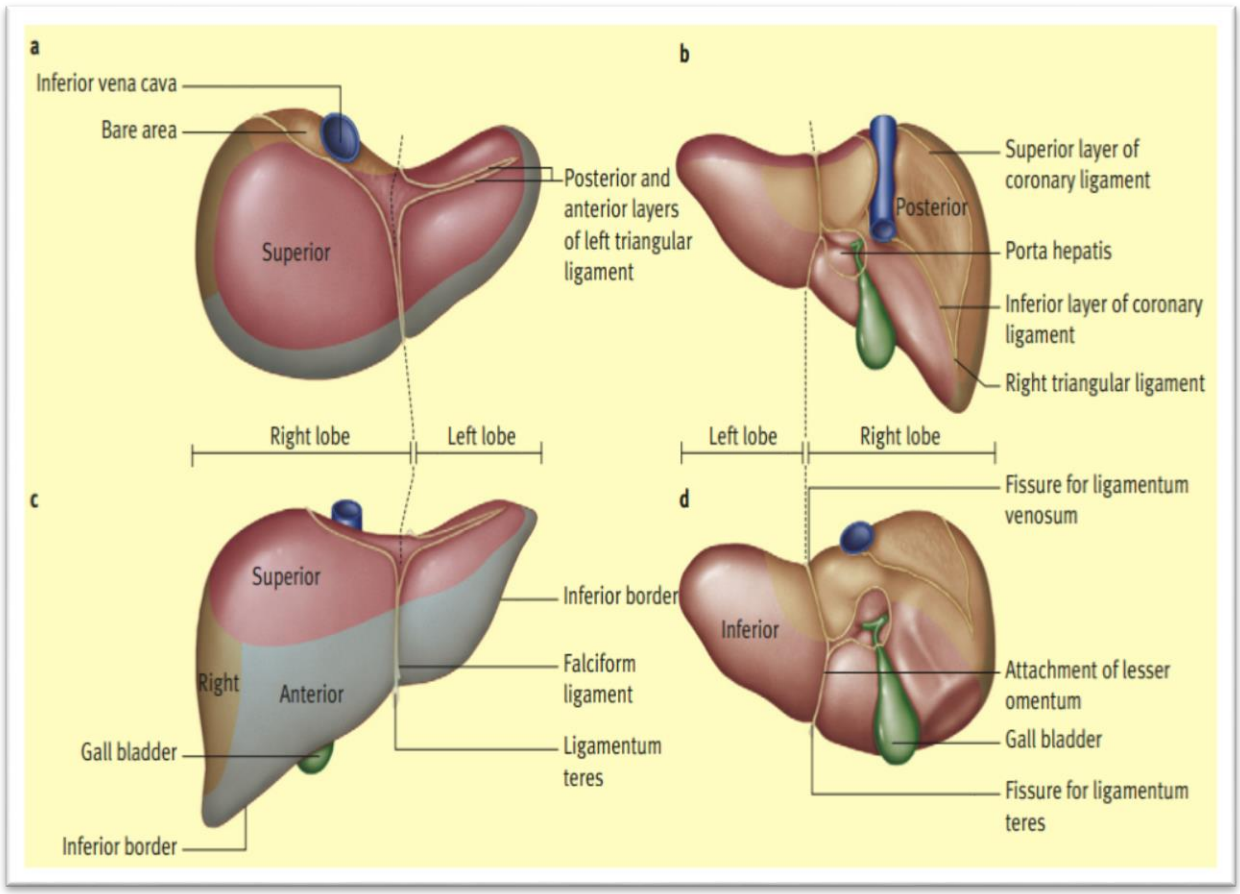


Figure 03 : The surface features, ligaments and peritoneal attachments of the liver. (Ellis, 2011).

I.1.*2.* Surfaces of the liver and their relations

The three surfaces of the liver in sagittal section are the posterior surface, the anterosuperior surface, and the inferior surface.

I.1.2.1.Posterior surface

The posterior surface is related to the vertical part of the diaphragm and, for all practical purposes, is retroperitoneal. Three anatomic entities are related to the posterior surface: the retrohepatic part of the IVC, the right adrenal gland, and the upper pole of the right kidney. The IVC travels through the hepatic parenchyma. The bare area of the liver may also be considered part of the posterior surface. (Skandalakis et al., 2004)

I.1.2.2.Anterosuperior surface

The anterosuperior surface is related to the diaphragmatic dome. To be more specific, the anterosuperior surface is located behind the ribs and cartilages, part of the diaphragm, pericardium, the pleurae, and the pulmonary parenchyma. This superior surface is covered by peritoneum except for the attachment of the falciform ligament and where, more dorsally, the superior reflection of the coronary ligament bounds the bare area of the liver. (Skandalakis et al., 2004) (Cotoi et al., 2015)

I.1.2.3.Inferior surface

The inferior surface is the visceral hepatic surface. It is related to several intraperitoneal anatomic entities and spaces. The space under the right lobe is the subhepatic space of Morison; the space under the left is the lesser sac. The inferior visceral hepatic surface under the right lobe is related to the gallbladder, right adrenal gland, right kidney, right renal vessels, head of pancreas, proximal part of the pancreatic neck, first and second parts of the duodenum, common bile duct, portal vein, hepatic artery, IVC, and hepatic colonic flexure (figure 04). (Skandalakis et al., 2004).

Additionally, the duodenum and portal structures are in direct association with the liver through the hepatoduodenal ligament (inferior aspect of the lesser omentum) and porta hepatis. (Abdel-Misih et al., 2010).

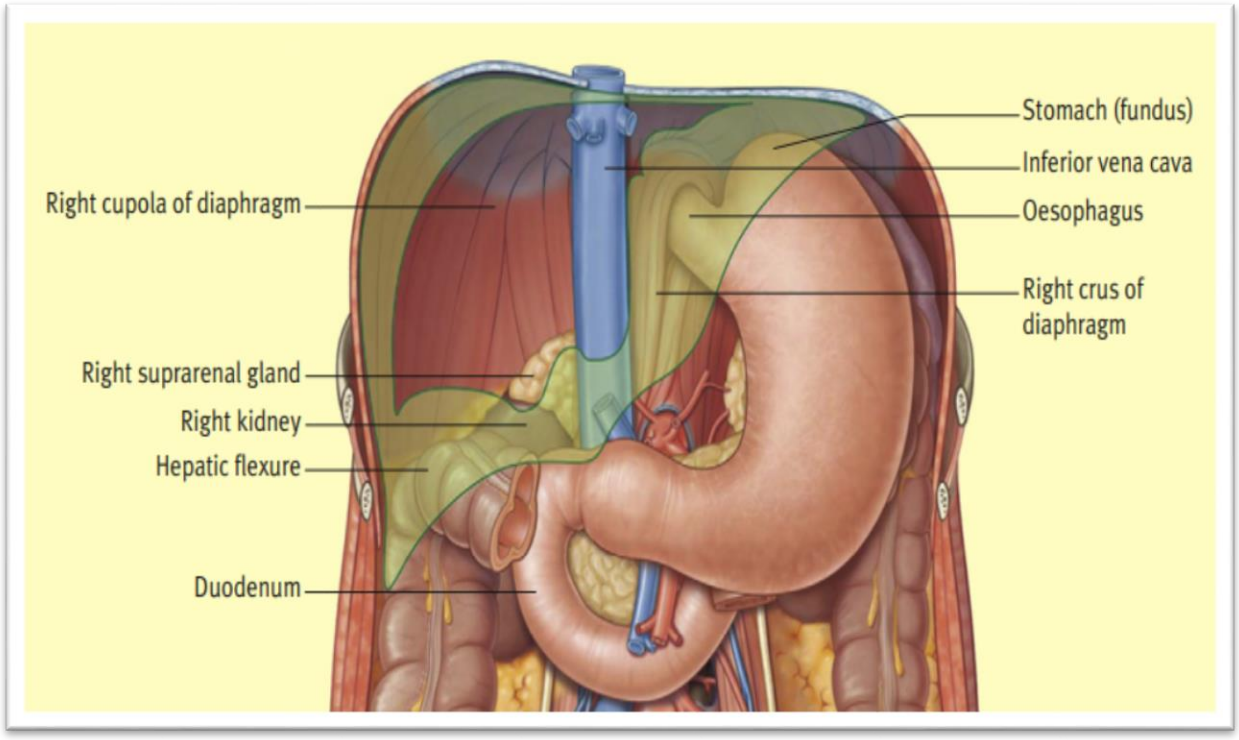


Figure 04: Liver position (Ellis, 2011).

I.1.3. Lobes and segments of the liver

Liver anatomy is described in terms of either its morphological anatomy or its functional anatomy:

I.1.3.1. Morphological anatomy

Based on the external appearance of the liver (figure 05):

- The liver is divided into the right anatomical lobe (much larger) and the left anatomical lobe by the falciform ligament. (Sibulesky, 2013**)** (chambers et al., 2019)
- When viewed from beneath, two additional small lobes can be seen between the right and left lobes. These are the caudate (posterior) and quadrate (inferior) lobes (chambers et al., 2019). The quadrate lobe is located on the inferior surface of the right

- Lobe The caudate lobe is located between the left and right lobes in an anterior and superior location. (Vernon H et al., 2020)

This morphological anatomy is not particularly useful when it comes to hepatobiliary surgery (chambers et al., 2019)

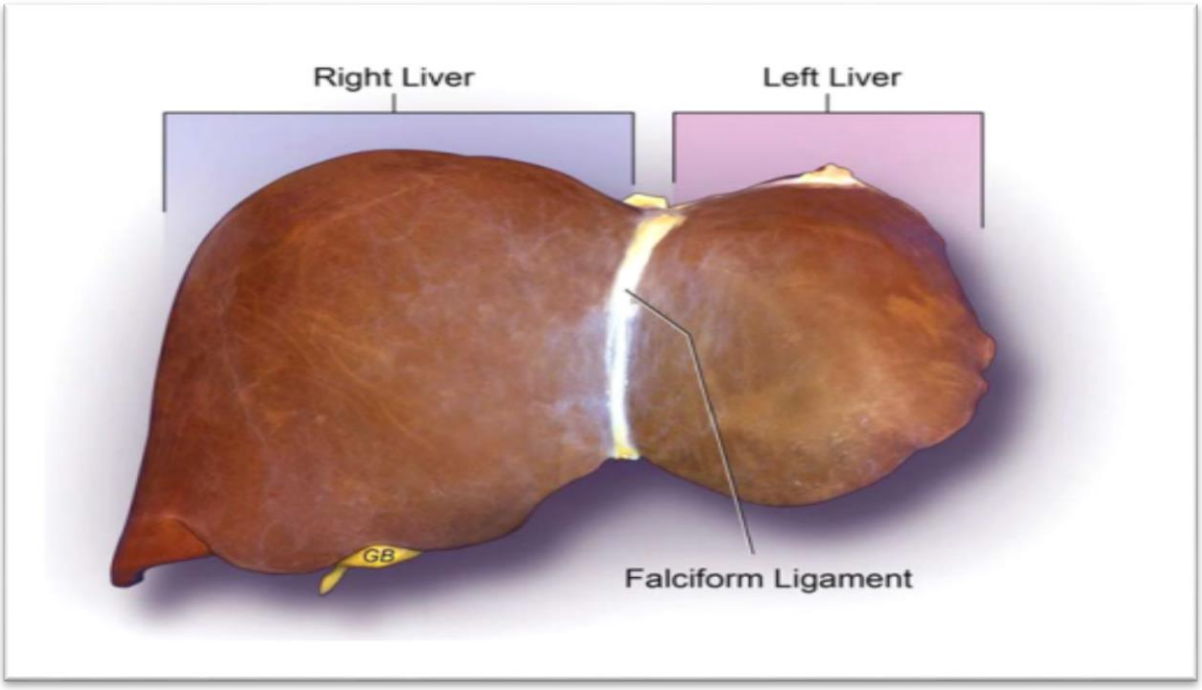


Figure 05: Morphological anatomy of liver. (Sibulesky, 2013)

I.1.3.2. Functional anatomy

The Couinaud classification divides the liver into eight functionally independent lobes (figure 06):

- Each of the eight lobes has its own blood supply derived from branches of the hepatic artery and portal vein, along with its own hepatic venous drainage and biliary drainage.
- The segments are numbered 1–8 in a clockwise direction, starting from the caudate lobe.
- The point where the portal vein, common bile duct and hepatic artery enter the liver is known as the hilum or porta hepatis.

- An imaginary line between the gallbladder fossa and inferior vena cava (called Cantlie's line) separates the functional right and left halves of the liver (this is not the falciform ligament). The vessels of the porta hepatis divide into right and left branches at this point.
- These segments, numbered from I to VIII, belong, for segments II, III and IV, to the left liver and for segments V, VI, VII and VIII to the right liver.
- Segment I, which receives unique vascularity and isolated venous drainage in the inferior vena cava, cannot be counted either inside the right liver or inside the left liver.
- Recently, an IX segment was added to the eight conventionally described; it is in fact the right part of segment I.
- Indeed, segment I is easily identifiable in its part located between the portal trunk and the inferior vena cava, behind the venous ligament of Arantius, but there is also an extension of this segment to the right, behind the right portal branch. However, the separation between segment I and IX remains theoretical and has few practical implications. (Lafortune et al., 2007).
- From a surgical perspective, the Couinaud classification is much more useful: any given lobe can continue its normal function when neighbouring lobes are resected. (chambers et al., 2019).

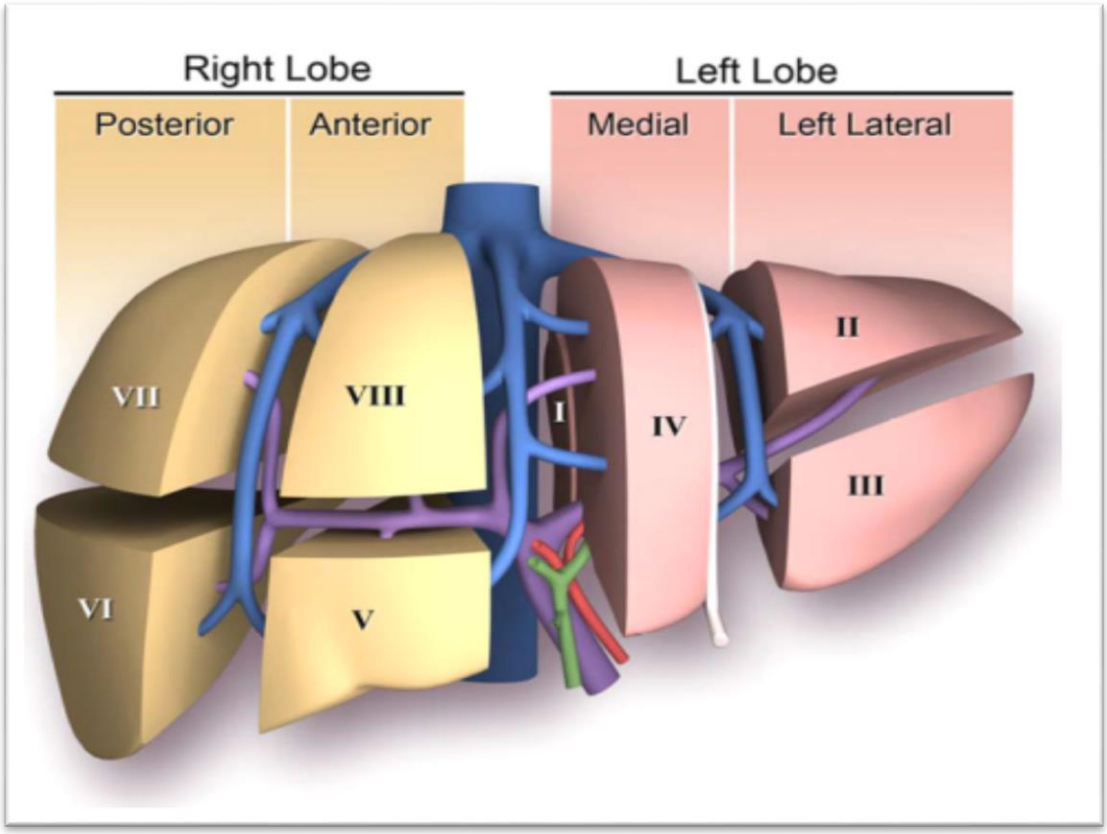


Figure 06: Functional anatomyof liver. (Sibulesky, 2013)

Table 01: Couinaud classification of the liver

Right lobe		Left lobe	
Right posterior section	Right anterior section	Left medial section	Left lateral section
Segments VI and VII	Segments V and VIII	Segment IV	Segments II and III

I.1.4. Blood supply of liver

The liver is a very vascular organ and at rest receives up to 25% of total cardiac output, more than any other organ**.** (Abdel-Misih et al., 2010). It receives its blood from two sources, the hepatic artery (25 per cent) and the portal vein (75 per cent). Blood is returned to the vena cava by way of the hepatic veins. (Kennedy et al., 1977)

In the liver, arteries, portal veins, and bile ducts are surrounded by a fibrous sheath, the Glissonian sheath. Hepatic veins in the hepatic parenchyma lack such protection .(Skandalakis et al., 2004). The arterial and portal blood ultimately mixes within the hepatic sinusoids before draining into the systemic circulation via the hepatic venous system. (Abdel-Misih et al., 2010).

I.1.4.1 Arterial Vasculature

- The common hepatic artery takes origin from the celiac trunk (86%); other sources are the superior mesenteric artery (2.9%), the aorta (1.1%), and, very rarely, the left gastric artery.
- The common hepatic artery then runs horizontally along the upper border of the head of the pancreas covered by the peritoneum of the posterior wall of the omental bursa.
- The gastroduodenal artery branches off the common hepatic artery posterior and superior to the duodenum. (Skandalakis et al., 2004)
- The gastroduodenal artery proceeds caudally to supply the pylorus and proximal duodenum and has several indirect branches to the pancreas. (Abdel-Misih et al., 2010).
- The common hepatic artery (figure 07) continues as the proper hepatic artery and turns upward to ascend in the lesser omentum, enveloped by the hepatoduodenal ligament, in front of the epiploic (Winslow's) foramen.
- Within the hepatoduodenal ligament, the proper hepatic artery lies to the left of the common bile duct and anterior to the portal vein. The portal vein, however, is located posteriorly or deeper to the proper hepatic artery and the common bile duct.
- Within the ligament the proper hepatic artery divides into right and left branches, called right and left hepatic arteries. Arterial distribution to different functional segments is identical to the distribution of portal vein.(Skandalakis et al., 2004)

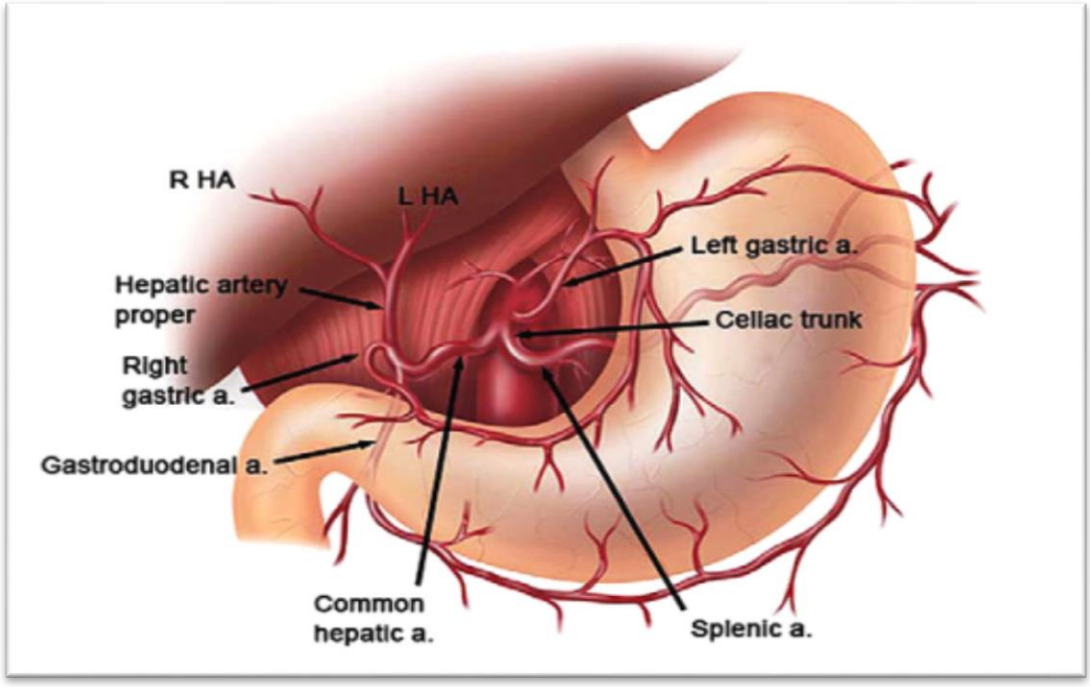


Figure 07: Common hepatic arterial configuration. (Abdel-Misih et al., 2010).

I.1.4.2. Venous Vasculature

I.1.4.2.1. Hepatic vein

The venous drainage of the liver is through the intrahepatic veins that ultimately coalesce into three hepatic veins that drain into the IVC superiorly (figure 08). The left and middle hepatic veins may drain directly into the IVC but more commonly form a short common trunk before draining into the IVC. The right hepatic vein is typically larger, with a short extrahepatic course and drains directly into the IVC. Additional drainage occurs directly into the IVC via short retrohepatic veins and, on occasion, an inferior right accessory hepatic vein. (Abdel-Misih et al., 2010)

The left hepatic vein accounts for 20.7% of the venous drainage and primarily drains the left lobe of the liver. The middle hepatic vein accounts for 32.7% of hepatic drainage and drains the middle portions of the left and right lobes of the liver.

The right hepatic vein accounts for 39.6% of drainage and drains the lateral portion of the right lobe of the liver.

The caudate lobe of the liver drains into the middle hepatic vein in most cases, though some cases drain directly into the retrohepatic portion of the inferior vena cava. (Vernon et al., 2020)

The hepatic veins within the parenchyma are unique in that, unlike the portal venous system, they lack the fibrous, protective, encasing the Glisson capsule.

The IVC maintains an important and intimate association with the liver as it courses in a cranial-caudal direction to the right of the aorta. As the IVC travels cranially, it courses posterior to the duodenum, pancreas, porta hepatis, caudate lobe, and posterior surface of the liver as it approaches the bare area where it receives the hepatic venous outflow from the hepatic veins. Multiple small retrohepatic veins enter the IVC along its course, mostly from the right hepatic lobe. (Abdel-Misih et al., 2010)

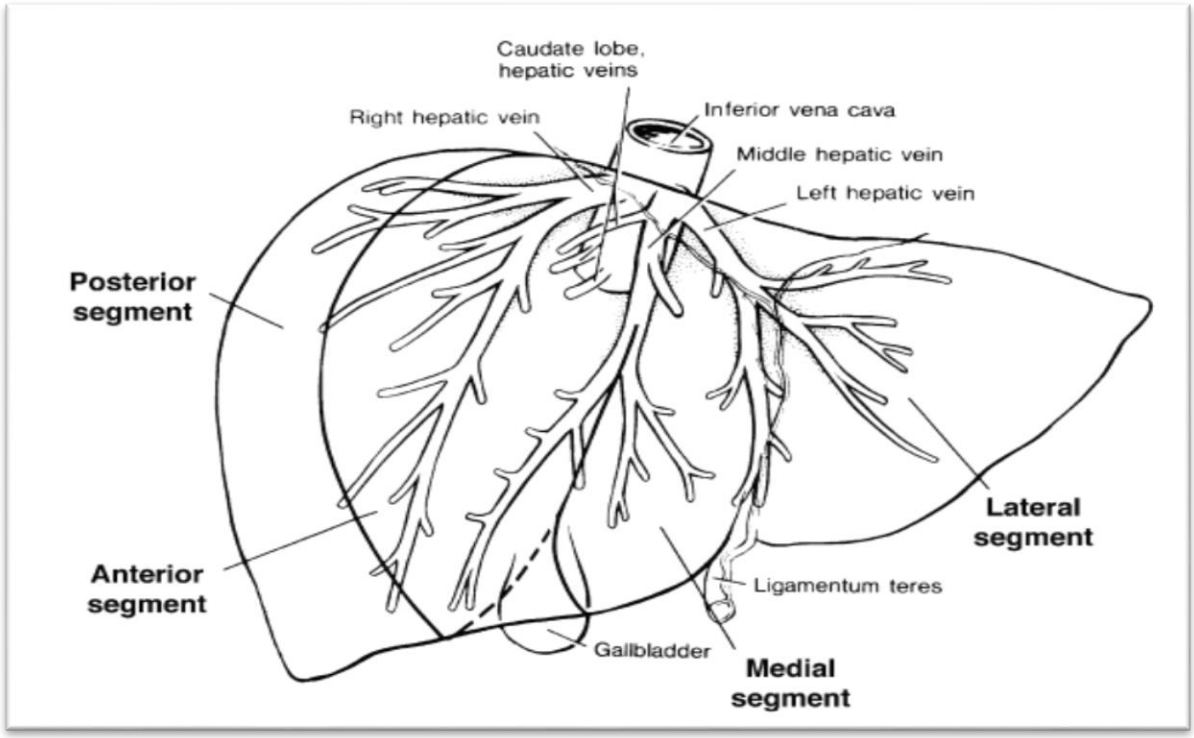


Figure 08: Diagram of the intrahepatic distribution of the hepatic veins. (Skandalakis et al., 2004)

I.1.4.2.2. Portal vein

The portal vein (Fig. 9, 10) returns blood to the liver from the mesenteric bed, the pancreas, and the spleenis (Kennedy et al., 1977), it is between 7 and 10 cm long and between 0.8 and 1.4 cm in diameter (Skandalakis et al., 2004) and is valveless and is a low-pressure system with pressures typically 3 to 5 mm Hg.

The portal vein is formed by the confluence of the superior mesenteric vein and the splenic vein behind the neck of the pancreas (figure 09) (Abdel-Misih et al., 2010) and emerges from behind the duodenum to course in the free fold of the gastrohepatic omentum. Additional venous branches that drain into the portal vein include the coronary (left gastric) vein, cystic vein, and tributaries of the right gastric and pancreaticoduodenal veins.

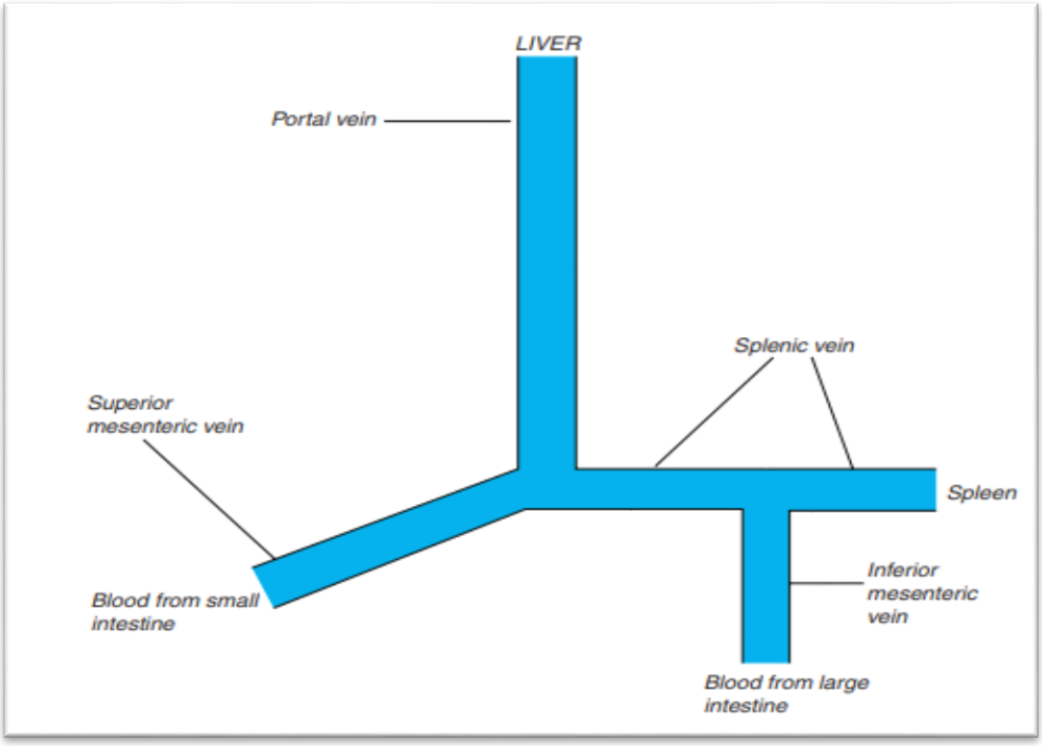


Figure 09: Portal venous system. (Virovic-Jukic et al., 2018)

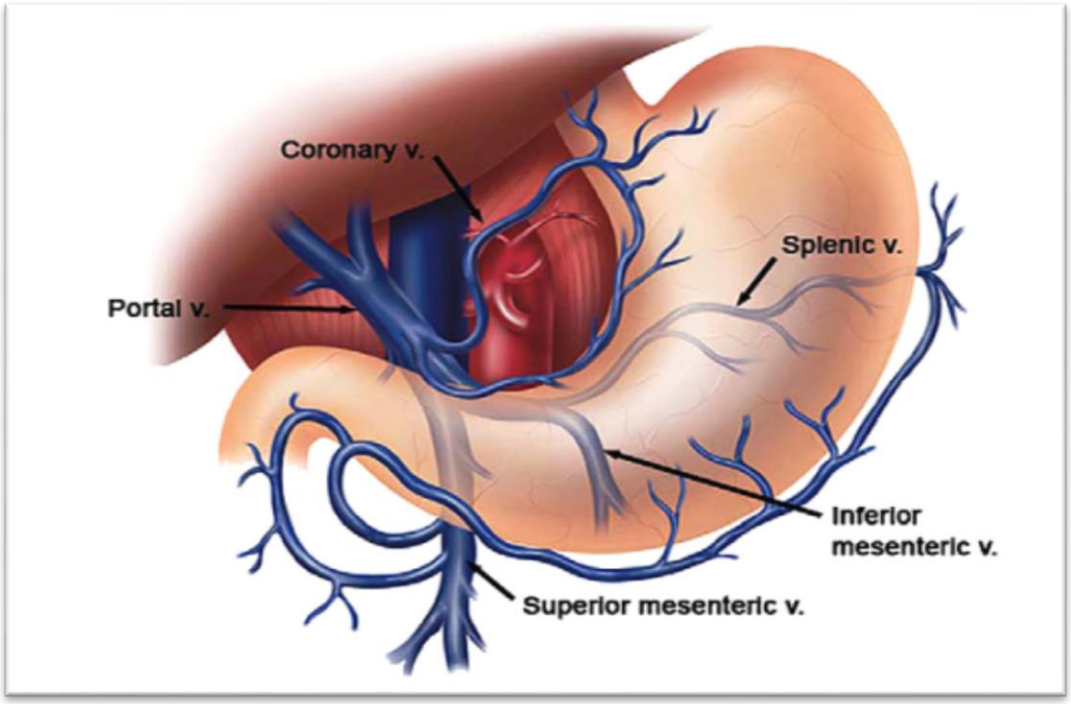


Figure 10: Hepatic venous vasculature inflow. (Abdel-Misih et al., 2010)

The main portal vein courses cranially toward the liver as the most posterior structure within the hepatoduodenal ligament to divide into the left and right portal veins near the liver hilum.

The left branch is longer and morphologically less effective as a channel of blood flow. The left portal vein has a transverse portion (figure 11), which lies in the hilum, and an umbilical part, which lies in the left segmental fissure. The transverse part of the left trunk is 2 to 3.5 cm in length. At this point, it bends in an anterolateral direction to form the umbilical portion, which immediately gives off a branch to the superior area of the lateral segment. (Kennedy et al., 1977).

Within the liver, the umbilical portion of the left portal vein commonly first gives off a branch to segment II before then dividing into branches to segment III and to segment IV. (Abdel-Misih et al., 2010)

The right branch of the portal vein measures approximately 2 to 3 cm in length (Kennedy et al., 1977) and is located anterior to the caudate process, Near its origin it gives off a branch for the caudate lobe. It follows the distribution of the right hepatic artery and duct

and bifurcates into anterior and posterior segmental branches to segments V and VIII and segments VI and VII, respectively as soon as it enters the hepatic parenchyma. (Abdel-Misih et al., 2010) (Skandalakis et al., 2004)

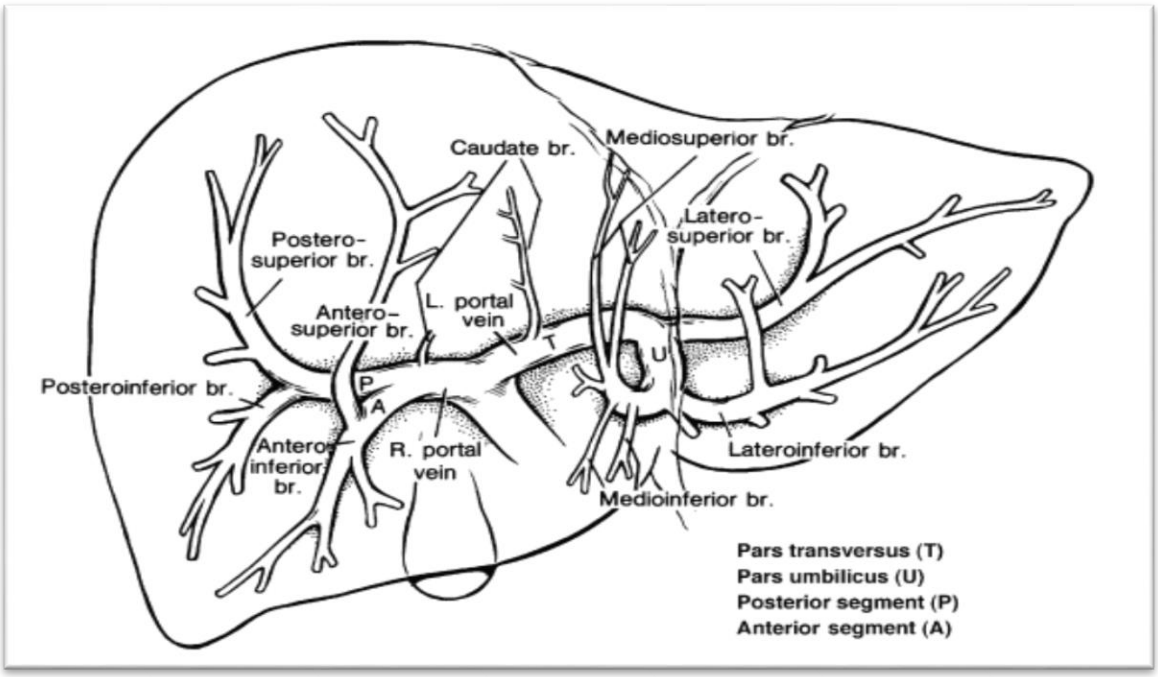


Figure 11: Intrahepatic distribution of the hepatic portal vein. A, anterior segment; br, branch; P, posterior segment; T, pars transversus; U, pars umbilicus, the site of the embryonic ductus venosus (Skandalakis et al., 2004)

I.1.5. Lymphatic network

The liver possesses a superficial and deep lymphatic network through which lymph produced in the liver drains. (Skandalakis et al., 2004)

The deep network is responsible for greater lymphatic drainage toward lateral phrenic nodes via the hepatic veins and toward the hilum through portal vein branches. The superficial network is located within the Glisson capsule with an anterior and posterior surface. The anterior surface primarily drains to phrenic lymph nodes via the bare area of the liver to join the mediastinal and internal mammary lymphatic networks. The posterior surface network drains to hilar lymph nodes, including the cystic duct, common bile duct, hepatic artery, and peripancreatic as well as pericardial and celiac lymph nodes. (Abdel-Misih et al., 2010)

I.1.6. Neural network

The neural innervation and controls of liver function are complex and not well understood. However, like the remainder of the body, the liver does have parasympathetic and sympathetic neural innervation. Nerve fibers are derived from the celiac plexus, lower thoracic ganglia, right phrenic nerve, and the vagi. The vagus nerves divide into an anterior (left) and posterior (right) branch as they course from the thorax into the abdomen. The anterior vagus divides into a cephalic and a hepatic division of which the latter courses through the lesser omentum (gastrohepatic ligament) to innervate the liver and is responsible for the parasympathetic innervation. Sympathetic innervation arises predominantly from the celiac plexus as well as the thoracic splanchnic nerves. (Abdel-Misih et al., 2010)

I.1.7. Biliary tree

The intrahepatic biliary tree (figure 12) is comprised of multiple ducts that are responsible for the formation and transport of bile from the liver to the duodenum and typically follows the portal venous system. (Abdel-Misih et al., 2010)

Union of ducts of segment II and III behind the umbilical part of left portal vein form the left hepatic duct (LHD) which then receives the duct from segment IV. Average length of the LHD is 1.7 cm and diameter is 3.0 mm (±1.08).

The right anterior sectoral duct (RASD) drains segments V and VIII and the right posterior sectoral duct (RPSD) drains segments VI and VII. The RPSD passes horizontally and generally curves round the RASD to join its medial side to form the right hepatic duct (RHD). Average length of RHD is 0.9 cm and diameter is 2.6 mm (± 1.2). Both right and left hepatic ducts drain the caudate lobe (segment I).

The right and left hepatic ducts unite in the hilar plate, close to the right end of porta, in front of right branch of portal vein, to form the common hepatic duct (CHD). Its lower end is defined by its junction with cystic duct, on its right margin in an acute angle, to form the common bile duct (CBD). Its length varies from 1.0 cm to 7.5 cm and average diameter is 4.0 mm. Cystic duct, 3–4 cm long with a mean diameter of 4.0 mm, runs posteroinferiorly and to the left to join the right border of CHD to form the CBD. (Babu et al., 2013).

The common bile duct proceeds within the lateral aspect of the hepatoduodenal ligament toward the head of the pancreas to drain into the duodenum through the ampulla of Vater. (Abdel-Misih et al., 2010).

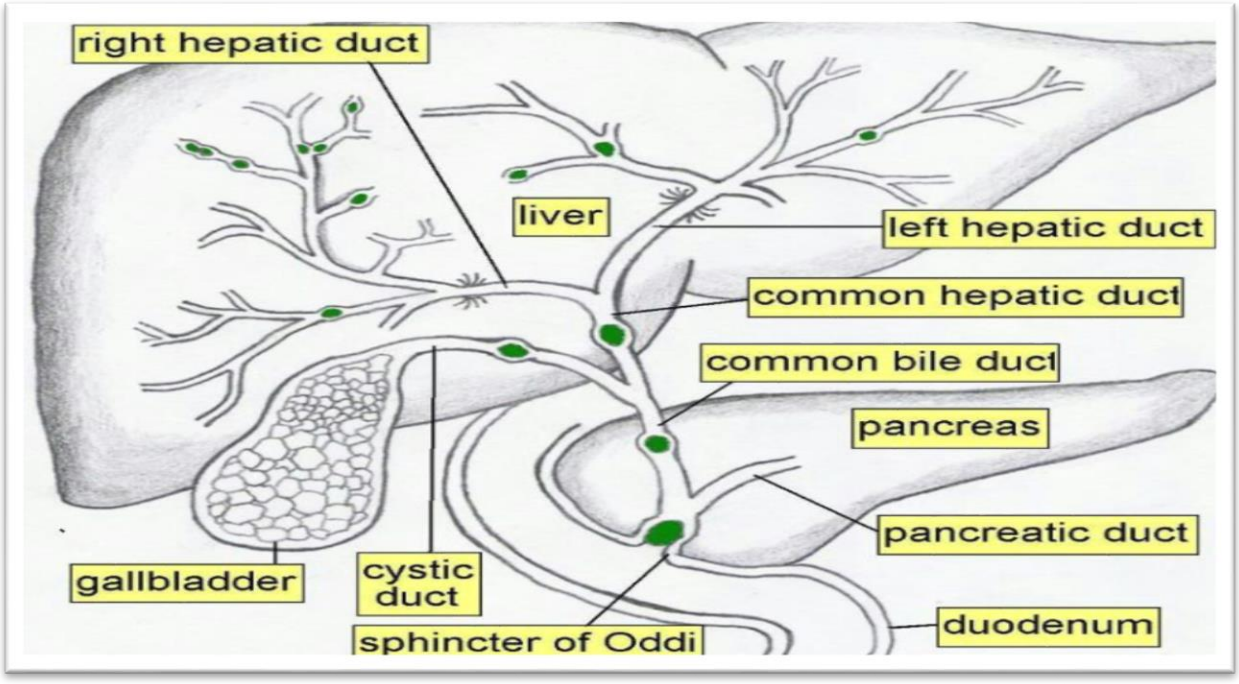


Figure 12 : Normal anatomy of biliary tree. (Babu et al., 2013)

I.2.Physiological roles of liver

The liver performs an enormous number of metabolic and synthetic functions. It plays a major role in carbohydrate, protein, and lipid metabolism. It is responsible for the synthesis and production of most of the plasma proteins, such as albumin, clotting factors, anticoagulants, and immune-related proteins. It produces and degrades various hormones and polypeptides, modifies alcohol, drugs and other toxic substances for their excretion, and is important in the homeostasis of iron metabolism. It is not surprising that such an important organ has a tremendous reserve capacity; up to 75% of the organ can be damaged or removed without causing death, because regeneration through compensatory hyperplasia rapidly restores liver function (Virovic-Jukic et al., 2018).

The functions of the liver are varied, and can be broadly classified as:

- Metabolic.
- Endocrine.
- Immunological.
- Hepatic clearance of drugs.
- Additional miscellaneous functions.

I.2.1. Metabolic functions

I.2.1.1.Protein Metabolism

The liver is responsible for protein metabolism, both synthesis and degradation. Unlike muscle cells, which synthesize proteins for their own use, hepatocytes synthesize proteins important for the whole organism. Hepatocytes are responsible for synthesis of most of the plasma proteins. Albumin, the major plasma protein, is synthesized almost exclusively by the liver. Also, the liver synthesizes other transport proteins (transferrin, ceruloplasmin, haptoglobin, lipoproteins) and many of the clotting factors necessary for blood coagulation (fibrinogen, prothrombin, factors V, VII, IX, X, XI, XIII, protein C, protein S, and antithrombin). The liver is the major site of production of immune related proteins (proteins of the complement system, acute-phase proteins) and thrombopoietin, a glycoprotein hormone that regulates the production of platelets by the bone marrow. Through the synthesis of coagulation factors and stimulation of platelet production, but also through synthesis and degradation of antithrombotic and fibrinolytic proteins, the liver plays the most important role in the maintenance of the coagulation system. The liver also produces insulin-like growth factor-1 (IGF-1), a polypeptide hormone that has anabolic effects and is an important regulator of growth in childhood. (Virovic-Jukic et al., 2018).

I.2.1.2. Carbohydrate Metabolism

The liver acts as a gate for the large amounts of glucose and other monosaccharides delivered from the gut (via the hepatic portal vein) during digestion, by storing them as glycogen, and is also the main source of glucose during starvation. Initially, glycogenolysis is the principal metabolic pathway used, but as the glycogen stores become depleted, gluconeogenesis assumes greater importance. The main substrates for this pathway are lactate,

pyruvate, volatile fatty acids, such as propionate, glucogenic amino acids (such as alanine from muscle), and glycerol (from lipolysis in fat stores). The control of carbohydrate metabolism is mainly hormonal (insulin, glucagons, catecholamines, and glucocorticoids). (Mair, 2017).

I.2.1.3. Lipid Metabolism

Lipid is the body's most efficient method of energy storage. The liver is involved in lipid metabolism in a number of ways:

- ***Lipid breakdown:*** Energy is extracted from free fatty acids as they are metabolised in a process called 'β-oxidation' within the hepatocyte mitochondria.
- ***Lipid synthesis:*** The liver synthesises triglyceride from excess glucose. Cholesterol is also synthesised in the liver. Cholesterol is used as a structural component of cell membranes and as a precursor for steroid hormone and bile salt synthesis.
- ***Lipid processing:*** Apolipoproteins are synthesised in the liver. These are involved in the packaging of cholesterol and triglyceride as low-density lipoprotein, very-low-density lipoprotein and high-density lipoprotein. (chambers et al., 2019)

I.2.1.4.Iron Metabolism

One of the liver functions is the regulation of iron homeostasis. The liver detects changes in systemic iron requirements and regulates iron concentrations. It is the major site for production of proteins that maintain systemic iron balance. The liver contains approximately 10% of total body iron stores, representing a main body store for iron, and is critical for the mobilization of iron to the circulation. Many proteins are involved in iron metabolism. Some proteins such as transferrin are the main transporters of iron in blood, which is stored in ferritin complexes in cells and contained in hemoglobin, myoglobin, cytochromes, and other enzymes which require iron for their functions. Iron homeostasis is regulated at a systemic level by balancing natural and excess iron loss with controlled absorption of dietary iron. (Virovic-Jukic et al., 2018).

I.2.1.5.Bile Acid Metabolism

Hepatocytes metabolize cholesterol to bile acids (cholic and chenodeoxycholic acid). These lipid-soluble bile acids are conjugated mainly to glycine or taurine molecules to form water-soluble conjugated bile acids, or bile salts, which serve as detergents in bile.

They are important physiological agents for intestinal nutrient absorption and biliary secretion of lipids, toxic metabolites, and xenobiotics. In the terminal ileum, bile acids present in the gut lumen are recuperated and returned to the liver, where they are taken up into hepatocytes and excreted into the bile again. This enterohepatic circulation retains over 95% of the bile acids. (Virovic-Jukic et al., 2018).

I.2.2. Endocrine functions

The liver has an array of endocrine roles:

- ***Secretion of hormones:*** including angiotensinogen, thrombopoietin, hepcidin and insulin-like growth factor 1 (IGF-1).
- ***Synthesis of hormone binding proteins:*** for example, thyroxine-binding globulin and sex hormone-binding globulin.
- ***Activation of hormones:*** thyroxine (T4) is converted into either the activated thyroid hormone triiodothyronine (T3) or inactivated (to reverse T3). Vitamin D undergoes the initial part of its activation in the liver (the 25- hydroxylation of cholecalciferol).
- ***Inactivation of hormones:*** the liver inactivates many hormones, including aldosterone, antidiuretic hormone and oestrogen. Insulin is worth a special mention: up to half of the insulin released by the pancreas into the portal vein is inactivated by the liver before it passes into the systemic circulation. (chambers et al., 2019).

I.2.3. Immunological functions

The liver is an extremely important immunological organ, with a number of roles:

- ***Phagocytosis:*** Ingested bacteria, viruses and parasites in the gastrointestinal tract pass into the portal vein and must travel through the liver before reaching the systemic circulation. These microorganisms are phagocytosed by the Kuppfer cells, specialised macrophages that line the sinusoids.
- ***Initiation of inflammation:*** Like other macrophages, Kuppfer cells can initiate an inflammatory response by the secretion of proinflammatory cytokines.
- ***Protein synthesis:*** In addition, the liver is a key part of the innate immune system, synthesising the complement proteins and C-reactive protein. (chambers et al., 2019).

I.2.4. Hepatic clearance of drugs

The liver is responsible for the detoxification (biotransformation) and clearance of many endogenous (e.g., ammonia, bilirubin, steroid hormones) and exogenous (e.g., plant toxins, insecticides, mercaptans) compounds and many drugs. In general, the more lipophilic and the higher the molecular weight, the more likely the substance is to be cleared by the liver rather than the kidneys. Such hepatic clearance usually involves metabolic biotransformation with or without conjugation. In liver disease, alterations of drug handling can induce clinically important consequences by changing drug concentrations and half-life. (Mair, 2017)

I.2.5.Additional miscellaneous functions

In addition to the many functions described above, the liver has a number of other functions:

- ***Storage:*** As well as storing glycogen, the liver is the main site of iron, copper and fat-soluble vitamin storage.
- ***Hematological:*** In the first trimester, the foetal liver is the main site of erythropoiesis. In addition, old or damaged RBCs are removed from the circulation by the liver's Kuppfer cells (though the spleen carries out the majority of this role).
- ***Blood reservoir:*** As discussed in Chapter 65, the liver can release up to 250 mL of venous blood into the systemic circulation in response to sympathetic stimulation. (chambers et al., 2019)

I.3. Liver Disease

I.3.1.Alcoholic Liver Disease (ALD)

Alcoholic liver disease (ALD) is one of the most prevalent liver diseases in Europe and the United States (Blachier et al., 2013) (Rehm et al., 2013). The disease can be caused by the chronic consumption of alcohol, the consumption of >40g of pure alcohol per day over a sustained period of time (years) leads to the highest risk of ALD (Bellentani et al., 2001).

ALD follows a well-recognized pattern of disease progression (Fig. 13). The spectrum of ALD begins with alcoholic fatty liver (AFL), which is characterized by hepatic steatosis (an accumulation of triglycerides in hepatocytes). Some individuals will progress and develop

hepatic inflammation, hepatocyte injury and ballooning, which is histologically defined as alcoholic steatohepatitis (ASH). ASH may progress slowly, with continual chronic liver injury and inflammation eventually leading to progressive fibrosis and cirrhosis, which ultimately may drive the development of hepatocellular carcinoma (HCC). In addition to this slow chronic progression, individuals with ALD (with or without cirrhosis) with rapidly progressing ASH may present with an acute clinical syndrome called alcoholic hepatitis, which is associated with poor prognosis (O'Shea et al., 2006) (Fig. 13). Alcoholic hepatitis in the presence of cirrhosis is referred to as acute-on-chronic disease. Prevention and treatment of ALD needs a multidisciplinary approach to manage alcohol use disorder (AUD) as well as nutritional, pharmacological and surgical interventions for decompensated (symptomatic) liver disease; (Mathurin et al., 2012)

The Global Burden of Disease (GBD) project estimated that there were 1,256,900 deaths in 2016 due to cirrhosis and chronic liver disease. Among those, 334,900 (27%) were attributable to alcohol (Naghavi et al., 2017). In addition, there were 245,000 deaths caused by HCC associated with alcohol, representing 30% of all HCC deaths (Akinyemiju et al., 2013).

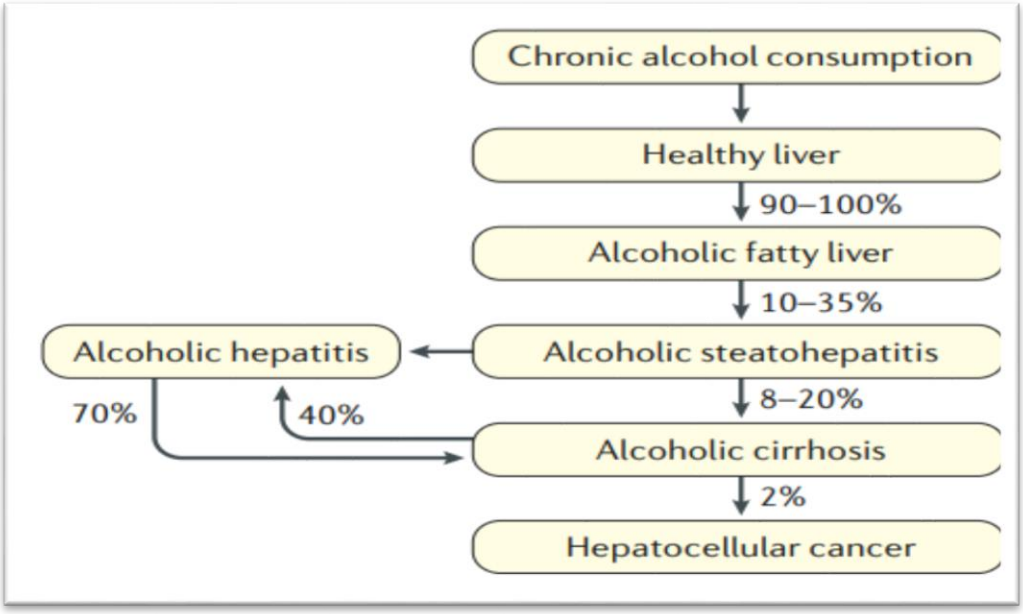


Figure 13: Natural disease course of alcoholic liver disease. (Seitz et al., 2018)

I.3.2.Nonalcoholic fatty liver disease (NAFLD)

Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome and is defined as the accumulation of fat in the liver in patients who do not consume excessive alcohol. (Angulo, 2002) NAFLD is asymptomatic in most affected patients and is associated with obesity and features of the metabolic syndrome, namely hypertension, dyslipidemia, central adiposity and insulin resistance (IR) or diabetes (Hassan et al., 2014),(Tsochatzis et al., 2008). The term NAFLD encompasses a wide spectrum of conditions, from simple accumulation of fat ('fatty liver' or steatosis) to steatohepatitis (NASH), fibrosis and cirrhosis with its clinical consequences (Tsochatzis et al., 2009). Despite its high prevalence, only a small proportion of subjects with NAFLD have NASH with consequent higher risk of liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC) (Fig. 14). While patients with simple fatty liver have similar life expectancy to the general population, those with NASH have an impaired survival, due primarily to cardiovascular and liver-related causes. (Angulo et al., 2015) (Ekstedt et al., 2012)

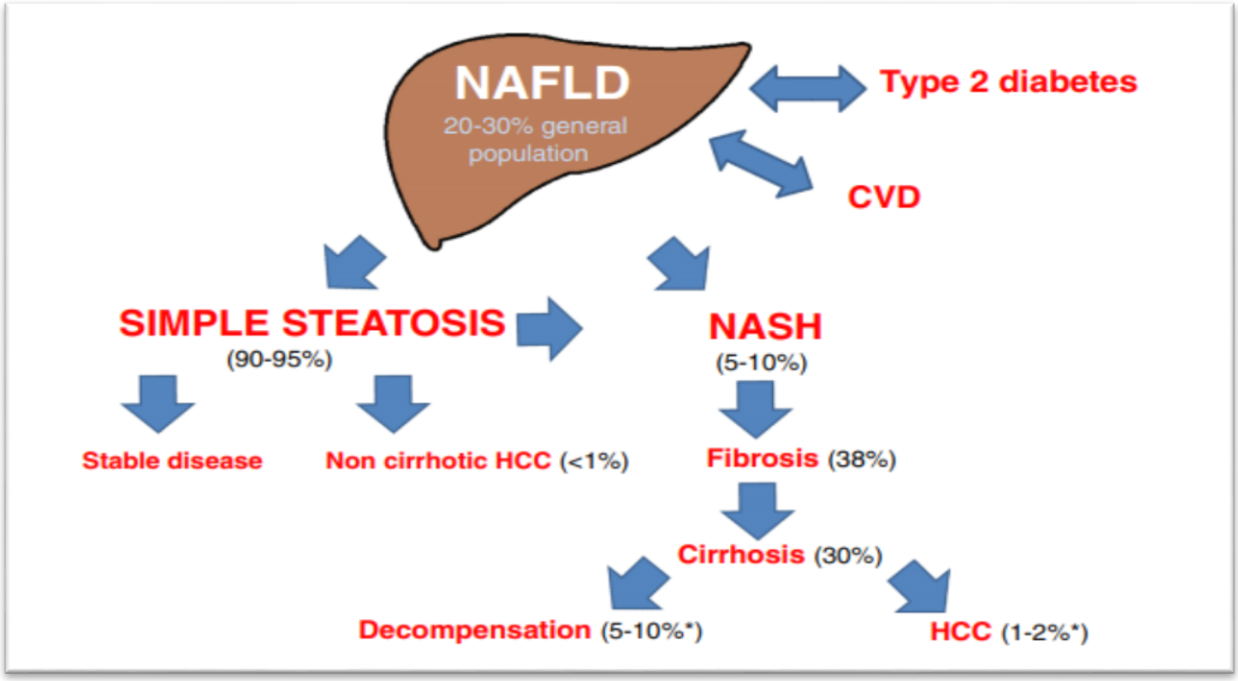


Figure 14: Natural history of NAFLD. (Buzzetti et al., 2016)

I.3.3. Autoimmune hepatitis (AIH)

Autoimmune hepatitis (AIH) is a chronic hepatocellular disease putatively caused by a loss of tolerance to hepatocyte-specific autoantigens (Manns et al., 2010) (Strassburg, 2013).The syndrome of AIH is characterized by elevated levels of aminotransferases, non-species specific autoantibodies, elevated γglobulin and/or IgG levels and interface hepatitis on liver biopsy. In accord with other autoimmune diseases, AIH is a global disease that afflicts children and adults of all ethnicities and races. The etiology of AIH is undefined but appears

to require immunogenetic susceptibility and environmental triggers that result in an unregulated immunological attack against hepatocytes. AIH is a rare cause of acute liver failure (ALF) but more often presents as an indolent, chronic liver disease. In untreated patients, AIH progresses at variable rates to cirrhosis with subsequent risks of complications of portal hypertension, liver failure or hepatocellular carcinoma (HCC). Patients who achieve remission using immunosuppressive drugs have an excellent prognosis (Heneghan et al., 2013) . In contrast, patients presenting with ALF and those presenting with or developing severe complications of cirrhosis or HCC require life-saving orthotopic liver transplantation (OLT). (Ilyas et al., 2011)

The pathophysiology of AIH is characterized by destruction of hepatocytes by T-cell and autoantibody-mediated molecules. Primary biliary cirrhosis is among these autoimmune diseases. (Reti et al., 2021).

I.3.4.Primary biliary cirrhosis (PBC)

Primary biliary cirrhosis is a slowly progressive autoimmune disease of the liver that primarily affects women. Its peak incidence occurs in the fifth decade of life, and it is uncommon in persons under 25 years of age. Histopathologically, primary biliary cirrhosis is characterized by portal inflammation and immune-mediated destruction of the intrahepatic bile ducts. These changes occur at different rates and with varying degrees of severity in different patients. The loss of bile ducts leads to decreased bile secretion and the retention of toxic substances within the liver, resulting in further hepatic damage, fibrosis, cirrhosis, and eventually, liver failure. Serologically, primary biliary cirrhosis is characterized by the presence of antimitochondrial antibodies, which are present in 90 to 95 percent of patients and are often detectable years before clinical signs appear. (Kaplan et al., 2005)

PBC has both genetic and environmental risk factors, and often it is associated with other autoimmune diseases such as Sjogren syndrome, autoimmune thyroid disease, Raynaud syndrome, scleroderma, hypothyroidism, and celiac disease.

The clinical manifestations of PBC include xanthomas, pruritus, hyperpigmented skin, jaundice, and fatigue. Laboratory fndings include elevated alkaline phosphatase/aminotransferases. (Reti et al., 2021).

I.3.5. Cirrhosis

Even though there are many etiologies of liver disease, the underlying pathophysiology is hepatic infammation and fbrosis leading to liver cirrhosis and ultimately liver failure. This process leaves patients with an inability to synthesize coagulation factors and metabolize toxic chemicals.

Cirrhosis results from different mechanisms of liver injury that lead to necroinflammation and fibrogenesis; histologically it is characterised by diffuse nodular regeneration surrounded by dense fibrotic septa with subsequent parenchymal extinction and collapse of liver structures, together causing pronounced distortion of hepatic vascular architecture.(Schuppan et al., 2008) (Dooley et al., 2011). This distortion results in increased resistance to portal blood flow and hence in portal hypertension and in hepatic synthetic dysfunction. Clinically, cirrhosis has been regarded as an end-stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma. (Tsochatzis et al., 2014).

I.3.6.Viral Hepatitis

Viral hepatitis, a significant health care burden worldwide, is defined as virally mediated liver inflammation. Numerous viruses are known to cause liver inflammation, including but not limited to, Epstein-Barr virus, Herpes simplex virus, and Cytomegalovirus. However, the hepatotropic viruses, termed A to E, are the most common culprits. Most of the hepatotropic viruses are acute and self-limiting, although forms B, C, and E have the potential to become chronic. Various genotypes of the viruses exist, with some being more prominent in specific geographical locations than others. Chronic hepatitis can lead to severe complications, namely cirrhosis, and hepatocellular carcinoma. Viral hepatitis and its complications result in

approximately 1 to 4 million deaths per year worldwide, by one estimate. The vast majority of deaths are caused by Hepatitis B and C. (Zarrin et al., 2021).

II.Hepatitis

II.1.Definition of hepatitis

Hepatitis is defined as inflammation of the liver that can result from a variety of causes such as heavy alcohol use, autoimmune, drugs, or toxins. However, the most frequent cause of hepatitis is due to a viral infection and is referred to as viral hepatitis. the most common types of viral hepatitis are Hepatitis A, Hepatitis B, and Hepatitis C. The other types of viral hepatitis are hepatitis D and E and are less frequently encountered (Zuckerman.2009).

Based on the etiology of hepatitis, the severity can range from mild and self-limiting to severe illness requiring liver transplantation. Hepatitis can be further classified into acute and chronic based on the duration of the inflammation/insult to the liver. If inflammation of the liver lasts for less than 6 months, then it is termed as acute hepatitis and if it lasts longer than 6 months it is termed as chronic hepatitis. Acute hepatitis is usually self-resolving but can cause fulminant liver failure depending on the etiology. In contrast, chronic hepatitis can cause liver damage that includes to significant morbidity and mortality (Dakhil.2009), (Ryder.2001).

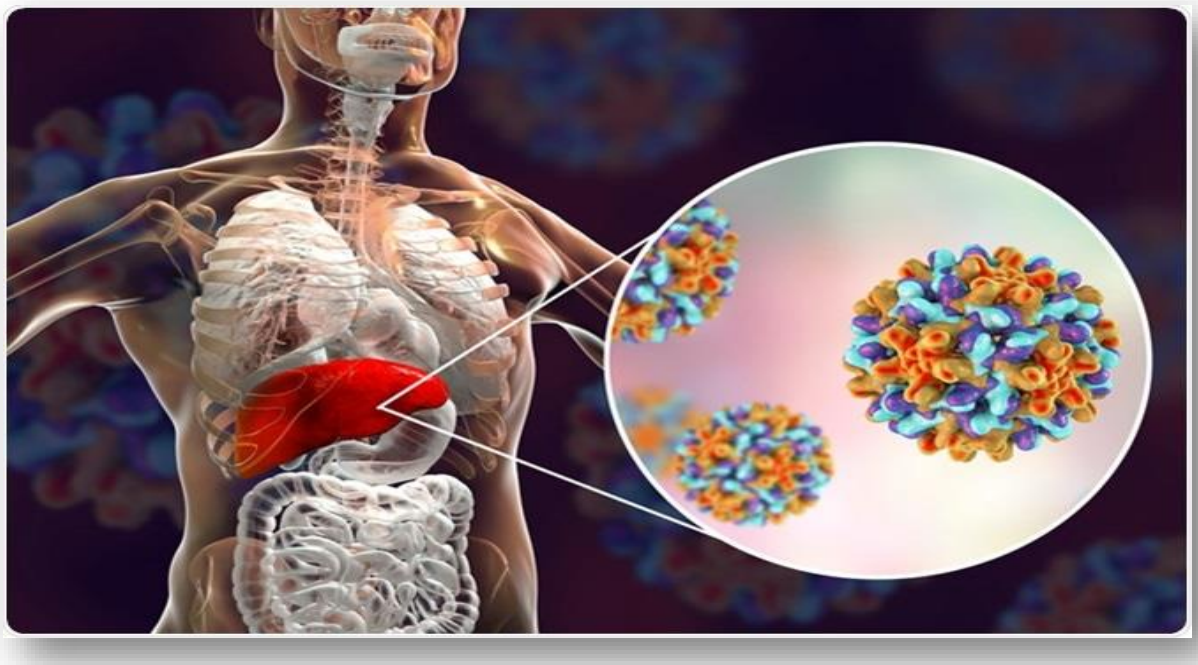


Figure 15: hepatitis viruses. (web site 01).

II.2. Types of Hepatitis viruses

Five viruses are specific agents of hepatitis. These are hepatitis A, hepatitis B and hepatitis C viruses, hepatitis Delta (or hepatitis D) and hepatitis E. Hepatitis F and G viruses, in particular fact, can be considered as agents specifically responsible for viral hepatitis. (Maiga, 2003).

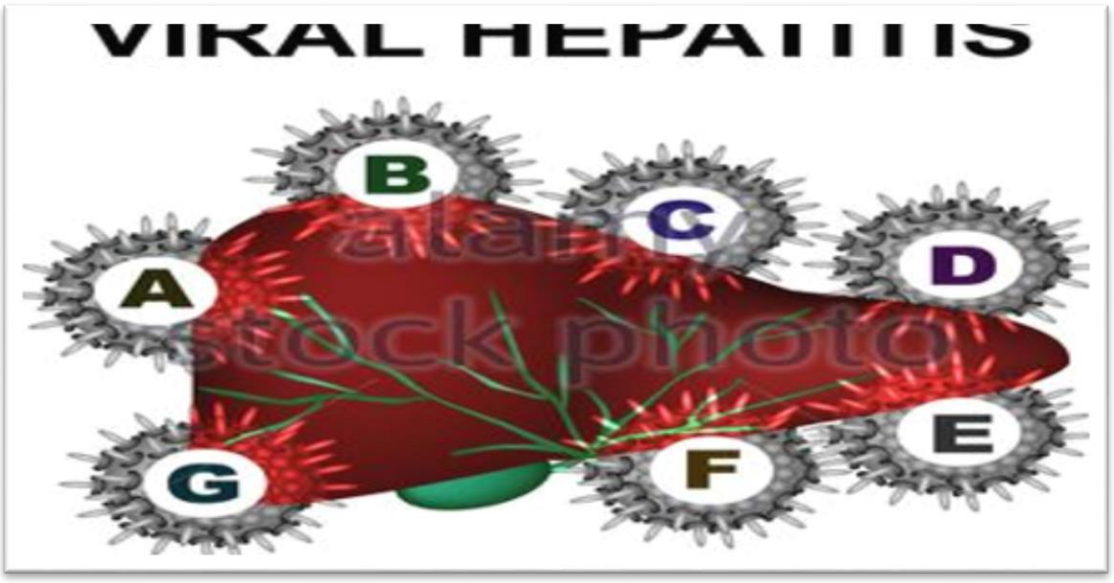


Figure 16: type of hepatitis virus. (web site 02)

II.2.1. Hepatitis A Virus (HAV)

Picornaviridae family, genus Hepatovirus. Single-stranded RNA virus. The icosahedral capsid of about 30 nm in diameter comprises 32 capsomers formed by the assembly of 4 structural proteins (VP1, VP2, VP3, VP4). The non-enveloped virus is very resistant in the external environment. The virus replication cycle is identical to that of other viruses of the Picornaviridae family. In humans, the virus multiplies in hepatocytes. In vitro multiplication on cell cultures is very difficult to obtain (Maiga .2003).

II.2.2. Hepatitis B Virus (HBV)

Hepatitis B virus is a DNA virus and is a member of the Hepadnaviridae family. The composition of the viral core is nucleocapsid, hepatitis B core antigen (HBcAg), which surrounds hepatitis B virus DNA, and DNA polymerase. The nucleocapsid is coated with the hepatitis B surface antigen (HBsAg), which is a viral surface

polypeptide. The gene that codes for hepatitis B core antigen (HBcAg), also codes for hepatitis B e antigen (HBeAg). Hepatitis B virus can be detected in serum, semen, vaginal mucus, saliva, and tears even at a lower level but not found in the stool, urine, or sweat. (You .2014).

II.2.3. Hepatitis C Virus (HCV)

Hepatitis C virus is an RNA virus and is a member of the **Flaviviridae** family with one serotype, but at least six major genotypes and more than 80 subtypes. The extensive genetic variability makes it challenging to develop a vaccine to prevent hepatitis C virus infection. Transmission can be parenteral, perinatal, and sexual, with the most common mode being the sharing of contaminated needles among IV drug users. Also, other high-risk groups include people who require frequent blood transfusions and organ transplantation of organs from infected donors. **(You .2014).**

II.2.4. Hepatitis D Virus (HDV)

Hepatitis D is an RNA virus and a single species in the **Deltavirus** genus. It contains the hepatitis D antigen and RNA strand and used HBsAg as its envelope protein; therefore, those who get hepatitis D virus infection have coinfection with the hepatitis B virus as well. Hepatitis D virus has similar modes of transmission as the hepatitis B virus, but perinatal transmission is uncommon. (Rizzetto .2015)

II.2.5. Hepatitis E Virus (HEV)

Hepatitis E is an RNA virus and a single species in the **Hepevirus** genus. The primary mode of transmission is Fecally contaminated water is the most common means, but person-to-person transmission is rare. However, occasionally maternal-neonatal transmission can occur as well (Pérez.2015).

II.2.6. Hepatitis G Virus (HGV)

Hepatitis G virus is an RNA virus and is a member of the **Pegivirus** A species of the Flaviviridae family. The primary mode of transmission is through infected blood and blood products. It is usually a coinfection in people who have chronic hepatitis B or hepatitis C infections. It is associated with acute and chronic liver disease, but research has not clearly established it as an agent that causes hepatitis by itself**.** (Soleiman .2015).

II.3. Hepatitis B

II.3.1. Epidemiology of viral hepatitis B

HBV infection is a serious global public health problem with about 250 million people chronically infected (Ganem.2004). It accounts for 500,000–1.2 million deaths per year and is the 10th leading cause of death worldwide. The prevalence of HBV infection varies markedly in different geographic and population subgroups. The area with the highest hepatitis B surface antigen (HBsAg) prevalence of >8% is Western sub-Saharan Africa, followed by Eastern sub-Saharan Africa, Central Asia, Southeast Asia, China and Oceania with a high intermediate prevalence of 5–7%; Latin America, Eastern Europe, North Africa, the Middle East, Turkey, Afghanistan, Pakistan, India and Australia with a low intermediate prevalence of 2–4% and the USA and Canada, Central America, Brazil and Western Europe with a low prevalence of <2% (**fig.01**) (Ott et al ,.2012) .

From 1990 to 2020, the prevalence of chronic HBV infection decreased on most regions. This was most evident in Central subSaharan Africa, Tropical and Central Latin America, Southeast Asia and Central Europe. Despite the decreasing prevalence, the absolute number of HBsAg-positive individuals increased from 223 million in 1990 to 240 million in 2020. The decline of HBV infection prevalence may at least in part be related to expanded immunization,suggested by the strongest decline found in South East Asian children (Ott et al ,.2012).

In the USA, the HBsAg or anti-HBC prevalence in adults changed little during the period of 1999–2006 compared to 1988–1994 while it significantly decreased in children, reflecting the impact of global and domestic vaccination (Wasley eet al.2010). In the USA, acute HBV infection has declined by 82% from 8.5 cases per 100,000 people in 1990 to 1.5 cases per 100,000 people in 2007, especially in children and adolescents (Wasley et al.2008).

Different from HCV (Bukh .1993) infection, the annual mortality rate from HBV infection in the USA did not change shown to be cost-saving in countries with high and intermediate endemicity. Apart from exposure prophylaxis through personal protection measures, HBV vaccination should be administered to all unvaccinated individuals traveling to areas with high or intermediate HBsAg prevalence (Mast et al.2006).

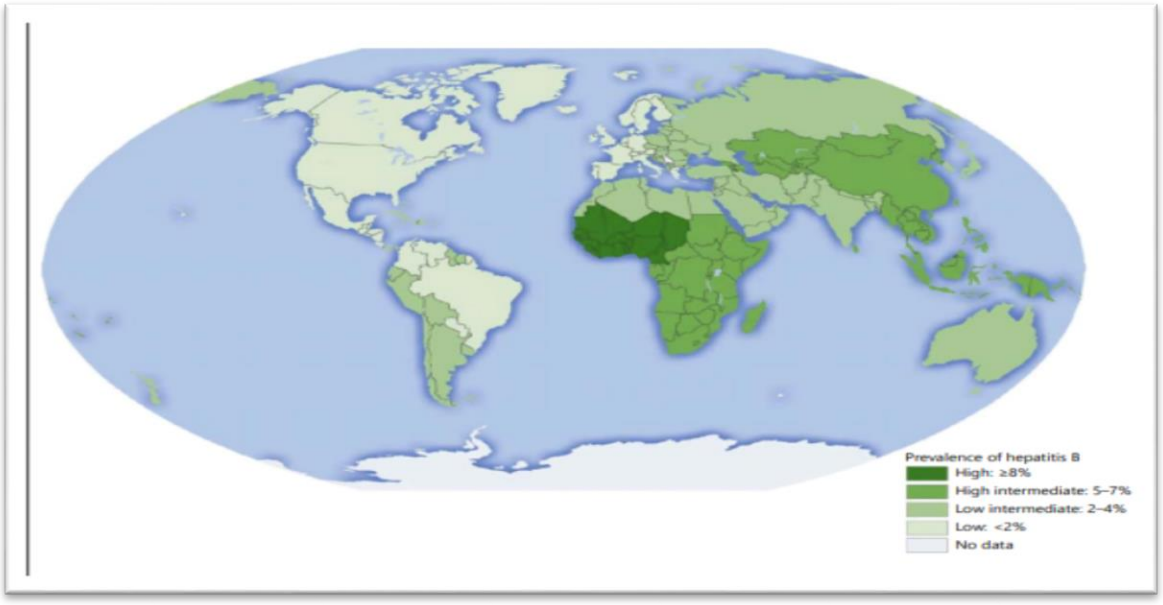


Figure 17: Worldwide prevalence of HBV infection. (web site 03)

II.3.2. Hepatitis B virus

II.3.2.1. Shapes of The HBV Particle

The hepatitis B virus is difficult to culture, but it was detected early on by electron microscopy thanks to the high concentration of viral particles in the serum of sick. Three types of structure can be observed (Dane .1970):

- Infectious viral particles 40 to 48 nm in diameter, called particles of Dane corresponding to full virions. They are the least frequent and are made up of a core (nucleocapsid containing a partially double-stranded DNA associated with a DNA polymerase) and an envelope **(Fig.04).**
- Spherical particles or spherules, very numerous, from 18 to 25 nm in diameter and filaments or tubules 22 nm in diameter by 50 to 250 nm in length which could be aggregate spheres. These last two elements have the same structure as the envelope viral and carry HBsAg. They consist of an envelope consisting of a bilayer lipid and have a diameter of 25 to 27 nm. These non-infectious spherules and filaments are excess products. (Tiollais .1985).

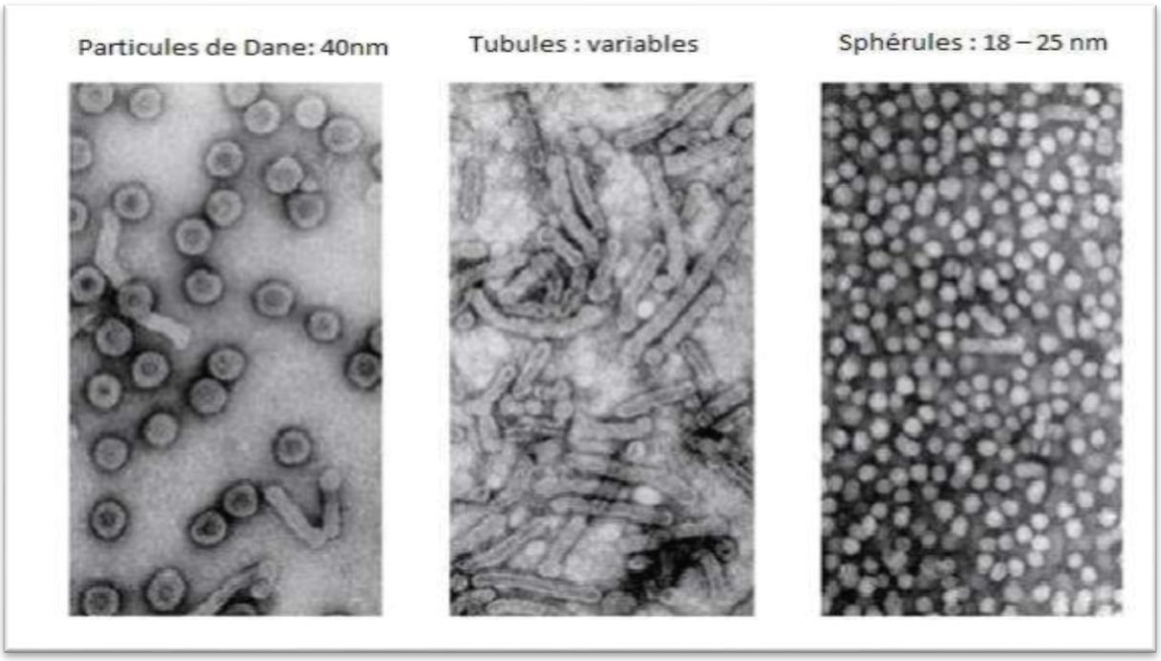


Figure 18: Electron microscopy photograph of viral particles. (Tiollais .1985)

II.3.2.2. Structure of The Virion

Dane particles are spherical structures with an external diameter approximately 42 nm circulating in the blood at a concentration of up to 1010 particles per ml in some patients. They correspond to infectious complete virions and consist:

- of a lipoprotein envelope acquired during budding from the reticulum endoplasmic and containing three viral surface proteins: L (for "large"), M (for "middle") and S (for "small"). These L, M and S proteins are present in the virus envelope in a 1: 1: 4 ratio (Heermann .1984).
- of an icosahedral nucleocapsid of approximately 27 nm formed by the assembly of 120dimers of a protein called Core (or HBcAg).
- of a single copy of the viral genome covalently associated with the polymerase viral. Studies also show the presence of cellular proteins such as protein serine kinases in these complete virions (Albin .1980

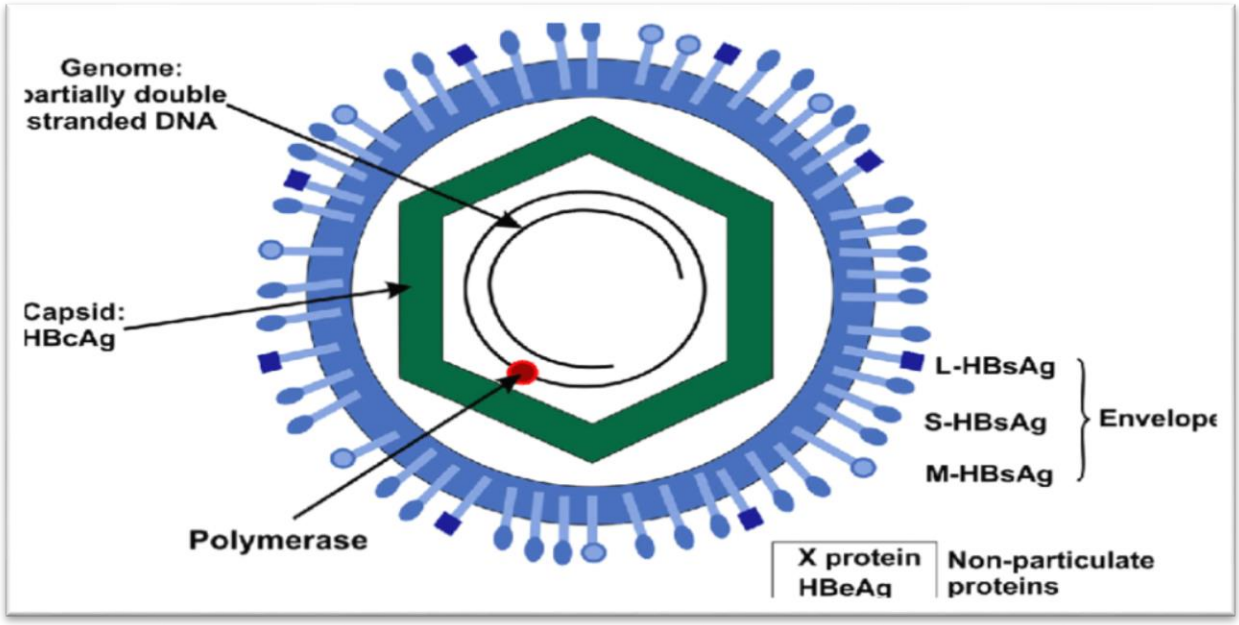


Figure 19: HBV Virus Structure (site web 04).

II.3.3. Types of Hepatitis According to The Lesion Aspect

Work-up for hepatitis B virus infection divides into work-up for acute infection and chronic infection.

II.3.3.1. Acute Infection

About two-thirds of patients with acute HBV infection have a mild, asymptomatic and subclinical illness that usually goes undetected. **(**Mcmahon.1985) Approximately one-third of adults with acute HBV infection develop clinical symptoms and signs of hepatitis, which range fom mild constitutional symptoms of fatigue and nausea, to more marked symptoms and jaundice, and rarely to acute liver failure. The clinical incubation period of acute hepatitis B averages 2–3 months and can range from 1–6 months after exposure, the length of the incubation period correlating, to some extent, with the level of virus exposure. (Barker.1972)

The incubation period is followed by a short preicteric or prodromal period of constitutional symptoms such as fever, fatigue, anorexia, nausea, and body aches. During this phase, serum ALT levels rise and high levels of HBsAg and HBV DNA are detectable. The preicteric phase lasts a few days to as long as a week and is followed by onset of jaundice or dark urine. The icteric phase of hepatitis B lasts for a variable period averaging

1–2 weeks, during which viral levels decrease. In convalescence, jaundice resolves but constitutional symptoms may last for weeks or even months. During this phase, HBsAg is cleared followed by the disappearance of detectable HBV DNA from serum.

Acute liver failure occurs in approximately 1% of patients with acute hepatitis B and jaundice. (Berk .1978) The onset of fulminant hepatitis is typically marked by the sudden appearance of fever, abdominal pain, vomiting, and jaundice, followed by disorientation, confusion, and coma. HBsAg and HBV DNA levels generally fall rapidly as liver failure develops, and some patients are HBsAg-negative by the time of onset of hepatic coma. Patients with acute liver failure due to hepatitis B require careful management and monitoring and should be referred rapidly to a tertiary medical center with the availability of liver transplantation **(**Gavilanes. 1982).

II.3.3.2. Chronique Infection

Chronic hepatitis B has a variable and dynamic course. Early during infection, HBeAg, HBsAg, and HBV DNA are usually present in high titers, and there are mild to moderate elevations in serum aminotransferase levels.

The overall prognosis of patients with chronic hepatitis is directly related to the severity of disease. For those with severe chronic hepatitis and cirrhosis, the 5-year survival rate is about 50%.35–37 Among patients with evidence of chronic hepatitis (elevated ALT and inflammation and/or fibrosis on liver biopsy), many are asymptomatic or have nonspecific symptoms, such as fatigue and mild right upper quadrant discomfort.

Patients with more severe disease or cirrhosis may have significant constitutional symptoms, jaundice, and peripheral stigmata of end-stage liver disease including spider angiomata, palmar erythema, splenomegaly, gynecomastia, and fetor hepaticus. Ascites, peripheral edema, encephalopathy, and gastrointestinal bleeding are seen in patients with more advanced cirrhosis. ALT and AST are often elevated but may not correlate well with severity of liver disease. Bilirubin, prothrombin time, and albumin often become abnormal with progressive disease. Decreasing platelet count is often a poor prognostic sign.

Patients with chronic hepatitis may develop acute exacerbations with markedly elevated serum ALT. This scenario is more frequently described in those with HBeAg-negative chronic hepatitis B. (Milich, 2003) To distinguish between acute hepatitis B and chronic hepatitis B with a flare, anti-HBc IgM is a useful marker, as described in the

previous section. However anti-HBc of the IgM class can be detected occasionally in patients with chronic hepatitis B with exacerbation. Alpha-fetoprotein (AFP), used as a marker for HCC, is often elevated in parallel with ALT during acute exacerbation.

However, it is unlikely to exceed 400 ng/mL. In patients with AFP much greater than this level, development of HCC should be suspected. An estimated one-third of persons with chronic HBV infection will ultimately develop a long-term consequence of the disease, such as cirrhosis, end-stage liver disease, or HCC. The determinants of outcome of chronic hepatitis B appear to be both viral (HBV DNA levels, HBV genotype, some HBV mutation patterns) and host-specific (age, gender, genetic background, immune status). **(**Spangenberg .2006)

II.3.4. Symptoms of Hepatitis B

Many other disorders can present with similar symptoms and signs commonly found in patients of hepatitis. Patients with acute and chronic active viral hepatitis infections usually present with discomfort, tired, low-grade fever, anorexia, loss of weight, nausea, vomiting.

- Patients can be completely normal on physical exam or may have right upper quadrant pain with hepatomegaly.
- urticarial rash and may show signs of dehydration.
- In advanced stages of liver disease from chronic viral hepatitis, patients may present with hematemesis, ascites, pedal edema, encephalopathy, etc.

These symptoms and signs are observable with many other acute or chronic infectious or non-infectious conditions. (Sagar,2019).

II.3.5. Diagnostic of Hepatitis B

HBV infection leads to a wide spectrum of liver disease ranging from acute hepatitis (including fulminant hepatic failure) to chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). (Hollinger .2001) The diagnosis of HBV infection and its associated disease is based on a constellation of clinical, biochemical, histological, and serologic findings. A number of viral antigens and their respective antibodies can be detected in serum after infection with HBV, and proper interpretation of the results is essential for the correct diagnosis of the various clinical forms of HBV infection **(Table 02).**

Table 02 : Hepatitis B serological and virological Markers

HBsAg	HBV infection, both acute and chronic
HBeAg	High-level HBV replication and infectivity; marker for treatment response
HBV DNA	Level of HBV replication; primary virologic marker for treatment response
Anti-HBc (IgM)	Acute HBV infection; could be seen in flare of chronic hepatitis B
Anti-HBc (IgG)	Recovered or chronic HBV infection
Anti-HBs	Recovered HBV infection or marker of HBV vaccination; immunity to HBV infection (titer can be measured to assess vaccine efficacy)
Anti-HBe	Low-level HBV replication and infectivity; marker for treatment response
Anti-HBc (IgG) and anti-HBs	Past HBV infection; could lose anti-HBs
Anti-HBc (IgG) and HBsAg	Chronic HBV infection
Anti-HBc (IgG) and/or anti-HBs and HBV DNA (PCR)	Latent or occult HBV infection

II.3.6. Traitement of Hepatitis B

The goal of treatment for chronic hepatitis B is to suppress HBV replication, prevent the progression of liver disease and thereby the development of cirrhosis, liver failure and HCC. (Sagar.2019).

- ***Interferon alpha (α-IFN):*** is the first-line treatment option for patients without cirrhosis. Interferon has antiviral, anti-proliferative and immuno-modulatory effects.
- At a dose of 100 mg daily, **lamivudine** leads to a marked reduction or elimination of detectable HBV DNA in plasma in about 40% of HBeAg positive and 60–70% of HBeAg negative patients.
- ***Telbuvidine*** :is a L-nucleoside analogue with potent anti-HBV activity. It is similar to lamivudine in mechanism of action and resistance profile but is more potent. However, its use is limited due to a high rate of resistance and cross-resistance with lamivudine.
- ***Emtricitabine:*** is another L-nucleoside analogue with similar activity to that of lamivudine.
- ***Adefovir:*** is a nucleotide analogue of deoxyadenosine monophosphate that has demonstrated efficacy in suppressing HBV DNA (20–50%) and normalizing liver function (50–70%).

- ***Entecavir:*** is a carbocyclic analogue of 2′ deoxyguanosine. It is a potent suppressor of HBV replication, resulting in loss of serum HBV DNA in 70–90%, and ALT normalization in 70–80% of patients.
- ***Tenofovir:*** is a nucleotide analogue initially approved for the treatment of HIV. It is often used in a coformulation with emtricitabine. After 48 weeks of therapy with tenofovir, HBV DNA loss is achieved in 80–90% and ALT normalization in 70–80% of patients.
- ***Orthotopic liver transplantation:*** is a treatment for chronic hepatitis B end-stage liver damage. However, the risk of reinfection on the graft is at least 80% with HBV presumably from extrahepatic reservoirs in the body.

II.3.7. Complications of Viral Hepatitis B

Complications of viral hepatitis include chronic infection with chronic active hepatitis, acute or subacute hepatic necrosis, cirrhosis, liver failure, and hepatocellular carcinoma in patients with hepatitis B or C infection. Patients who have hepatitis B infection are at high risk of developing chronic infection. Patients are also at significant risk of developing hepatocellular carcinoma, which is responsible for 45% of primary liver cancer worldwide. About 1% of patients can also develop fulminant hepatic failure, and the mortality rate is about 80% in those patients. About 75 to 85% of patients who get infected with hepatitis C end up developing chronic infection and about 20% of those patients end up developing cirrhosis and eventually hepatocellular carcinoma.

Cirrhosis itself can cause multiple complications, including hepatic encephalopathy, portal hypertension, ascites, spontaneous bacterial peritonitis, variceal bleed, hepatorenal syndrome, etc. Patients who have chronic hepatitis C infection also have a high risk of developing extrahepatic complications including cryoglobulinemia which can lead to rash, vasculitis, and glomerulonephritis secondary to deposition of immune complexes in the small vessels, non-Hodgkin lymphoma, focal lymphocytic sialadenitis, autoimmune thyroiditis, porphyria cutanea tarda, lichen planus, etc. (Zeuzem .2016).

II.3.8. Preventive and Patient Education

Patient education is key to preventing and controlling hepatitis, especially viral and alcoholic hepatitis. Patients who have viral hepatitis must obtain education educated regarding

the importance of routine follow-up and the importance of monitoring the disease progression and development of complications. Vaccination is your best protection against hepatitis B. The hepatitis B vaccine is safe and effective in protecting against hepatitis B infection, providing protection in 95 in 100 vaccinated people.

III.Oxidative stress

III.1.Definition of oxidative stress

Oxidative stress is defined as an imbalance in the balance between antioxidants and pro-oxidants in favor of antioxidants.There is a complex interaction between antioxidants and oxidants such as reactiveoxygen species, which modulates the generation of oxidative stress.(Derouiche et al,.2018).The over production of free radicals can cause oxidative damage to biomolecules (lipids, proteins, DNA),and The highly reactive oxygen species (ROS) are capable of damaging various structures and functional pathways in cells.(Nour El-Houda et al., 2020). eventually leading to many chronic diseases such as cancer, diabetics, cardiovascular diseases, chronic inflammation. (Samir et al., 2020).

III.2. Free radicals

Free radicals are any atoms which have independent existence and contain one or more unpaired electrons in their outer valence shell. ROS is two types, **radicals** [Superoxide (O2.-), Hydroxyl (. OH) Peroxyl (RO2.) Alkoxyl (RO.) Hydroperoxyl (HO2.)] and **Non-Radicals** [Hydrogen peroxide (H2O2) Hypochlorous acid (HOCl-), Ozone (O3),Singlet oxygen(1O2) and Peroxynitrite(ONOO-)] (Akhilesh.2014).

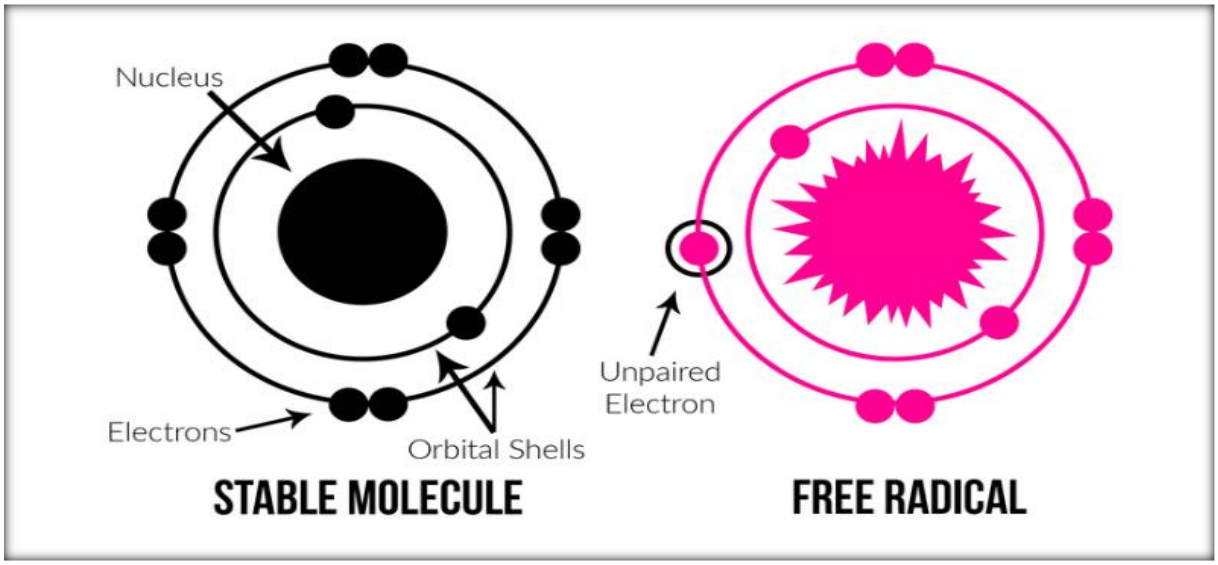


Figure 20: free radicals. (web site 05)

Table 03: Reactive oxygen species. (Rahman .2012)

Radicals	Non-radicals
Superoxide: O_2^-	Hydrogen peroxide: H_2O_2
Hydroxyl: OH^-	Hypochlorus acid: HOCL
Peroxyl: RO_2^-	Hypobrromus acid: HOBr
Alkoxyl: RO^-	Ozone: O_3
Hydroperoxyl: HO_2^-	Singlet oxygen: Δg

III.3. Sources of free radicals

III.3.1. Exogenous source

There are various source of production of ROS such as Radiation (UV light, x-rays, gamma rays), Chemicals that react to form peroxides (Ozone and singlet oxygen), Chemicals that promote superoxide formation(Quinones, nitro aromatics, bi pyrimidiulium herbicides), Chemicals that are metabolized to radicals (Poly halogenated

alkanes, phenols, aminophenol), Chemicals that release iron (ferritin etc.) Above exogenous source of ROS formation occurs by the Fenton's and Haber's reaction. (Haber.1934)

III.3.1.1. Fenton's reaction

Molecular oxygen reduced to form superoxide which has the ability to form more and highly Reactive Oxygen Species and superoxide's dismutation forms hydrogen peroxide. (Haber.1934)

O-2 + O-2 + 2H ⟶ H2O2 + O2 H2O2

react with transition metals such as Iron (Fe++) /Copper (Cu+) to form highly reactive hydroxyl radicals

Fe 2+ + H2O2 ⟶ Fe3+ + OH + OH-

III.3.1.2. Haber-Weiss reaction

H2O2 is more stable than superoxide, permeable to plasma membrane and plays two important roles in the body, either it is scavenged by enzymes Catalase /GSH(glutathione peroxidase), or it helps in the formation of ROS. (Phaniendra.2013). H2O2 is generated from transformation of the superoxide anion enzymatically (superoxide dismutase) and non-enzymatically. The most important reaction of H2O2 with free or poorly ligated Fe (II) is the Fenton reaction, generating highly reactive hydroxyl ions. Fe (II) by reacting with unsaturated fatty acids in the presence of H2O2 can initiate lipid peroxidation in biological membranes and lipoproteins producing HO.(Samir et al., 2020).

O2 + H2O2 ⟶ O2 + OH- + .OH

H2O2 reacts with Halogen atoms such Cl-, Br-, and I- and is utilized by Myeloperoxidase to form more reactive hypochloric acid / hyper chlorite. This is important for protein aggregation and fermentation.

H2O2 + Cl- ⟶ HOCl + OH

III.3.2.Endogenous sources of ROS

In the human body various enzymes such as monoamine oxidase, Lipoxygense

Cyclooxygenase, NADPH oxidase, Cytochrome P450 Monooxygenase, Xanthine oxidoreductase and Nitric oxide synthase present which responsible for the generation of ROS under sub cellular. (Phaniendra.2013).

III.3.2.1.Monoamine Oxidase

Under normal physiological condition in inner mitochondrial membrane Electron Transport chain produces ATP and superoxide. While in outer mitochondrial membrane monoamine oxidase haem containing enzyme present which catalyzes oxidative deamination of amines and produces H2O2 in matrix and cytosol. (Phaniendra.2013)

III.3.2.2.Xanthine Oxidoreductase

This enzyme catalyzes hypoxanthine into Xanthine, then into uric acid. Xanthine Oxidoreductase (XOR) is present in the form of Xanthine Dehydrogenase (XD); these two forms of Xanthine are transformed. XD is transformed into XO, irreversibly by proteolysis and reversibly by oxidation of sulfhydryls, and produce large amount of H2O2 and O2-It is also found that XOR can transform nitrates into nitrites and NO. It also catalyzes the NO with O2- and form highly reactive Peroxynitrite. (Phaniendra.2013)

III.3.2.3. Cytochrome P450 Oxidase

It is a haem-containing enzyme which present in mitochondria and participates in metabolism of cholesterol, hormones, steroids, catabolism of bile acids, arachidonic acid, eicosanoids, hydroxylation of vitaminD3 and retinoid acid by catalyzing intramolecular transfer of oxygen. (Phaniendra.2013)

III.3.2.4.Myeloperoxidase

Myeloperoxidase is haem containing enzyme, present in Neutrophils and eosinophils. It catalyzes the H2O2 with various substrates to form highly reactive hypochloric acids. (Phaniendra.2013)

III.4.Antioxidant

Types of Antioxidant Antioxidants may be enzymatic and non-enzymatic in nature in which enzymatic system directly or indirectly help in defence against the ROS.

III.4.1.Antioxidant Enzymatic

Several enzymes obstruct free radicals' formation, some of them act directly in scavenging ROS (primary enzymes), whereas "secondary enzymes" play an indirect role by supporting other endogenous antioxidants. This is the case, for instance, for glucose-6-phosphate dehydrogenase that regenerates NADPH, essential for primary enzyme action. (Banafsheh .2016)

III.4.1.1.Superoxide Anion Dismutation (SOD)

Primary enzymes act directly on the main ROS arising from incomplete O_2 reduction, O_2^- and H_2O_2. SOD scavenges the former, whereas CAT and GPX remove the latter. SOD (**E.C. 1.15.1.1)** is a metalloenzyme, catalyzing superoxide anion dismutation to H_2O_2 and molecular oxygen, as shown in reaction 1 (Singh, 2017). In turn, H_2O_2 can be removed by the other enzymatic antioxidant systems. (Singh, 2017)

$$\mathbf{2O2+2H+\rightarrow H2O2+O2\ (1)}$$

SODs can be divided into four groups, with different metal cofactors. Copper-zinc SOD is most abundant in chloroplasts, cytosol and extracellular space. Iron SOD is found in plant cytosol and in microbial cells, whereas manganese SODs are mitochondrial (Perera et al., 2017). SOD also competes for superoxide anion with NO. Therefore, SOD also indirectly reduces the formation of another deleterious ROS, peroxynitrite ($ONOO^-$, reaction 2), and increases the NO biological availability, an essential modulator for endothelial function. (Perera et al., 2017).

$$\mathbf{O-2\cdot+NO\cdot\rightarrow ONOO-\ (2)}$$

III.4.2.Antioxidant Non-Enzymatic

Some chemical molecules of low-molecular-weight can also directly act as antioxidants. In this case, their action is not catalytic, always needing antioxidant regeneration or its supply from the diet. Non-enzymatic antioxidants can therefore be divided into endogenous (if the eukaryotic cell is able to synthesize it) and exogenous (if the antioxidant needs to be ingested mandatorily through the diet). (Banafsheh .2016).

III.4.2.1.Endogenous Non-enzymatic Antioxidants

III.4.2.1.1.Glutathion Réduit (GSH)

GSH can act also act potent ROS scavengers (including ·OH, H2O2, organic peroxides, and ONOO–) directly, without enzymatic help. It is a tripeptide possessing a sulfhydryl (SH) group widely distributed in all tissues and organs. Its sulfhydryl (SH) group can interact with free radicals which limits their undesirable effect, these elements (GSH) can also be incorporated into enzymatic detoxification reactions against ROS as cofactor of several enzymes.(Derouiche et al,.2017). GSH plays several roles in cellular processes, including apoptosis, cell growth, and defense against oxidative stress. (Derouiche et al., 2019)

III.4.2.2.Exogenous Non-enzymatic Antioxidants

Exogenous antioxidants need to be supplemented continuously through the diet since their synthetic pathways are usually present only in microbial or plant cells. Vitamins, two of which show prominent antioxidant effects, such as vitamins C and E, belong to essential class of molecules. (Mirończuk-Chodakowska .2018)

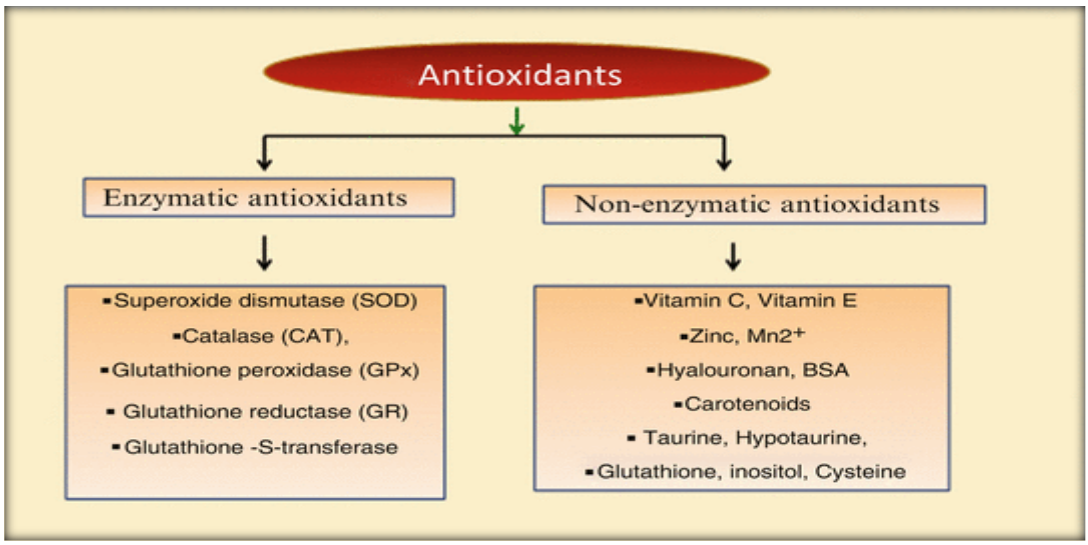


Figure 21: Enzymatic and non-enzymatic classification of antioxidants. (web site 06)

III.5. Oxidative stress and hepatitis

Intracellular parasitic viruses may remain clinically latent and without reactivation within host cells until the cellular redox balance is disturbed. Wide fluctuations in incubation periods for hepatitis B and C suggest that the viral activity can be determined by the redox

state of cells. With more severe oxidative stress, the viral replication is more active with dispersion from lysed or apoptotic cells. (Esrefoglu, 2012)

Viruses use host cell synthetic processes for replication, leading to the disturbance of the normal physiological biochemistry of endoplasmic reticulum and mitochondria with augmented ROS generation and antioxidant depletion. ROS play an important role in the pathogenesis of inflammatory diseases, although the detailed mechanisms of ROS involvement are still controversial (Esrefoglu, 2012). The ensuing redox imbalance and oxidative stress (OS) causes parenchymal damage ranging from subclinical anicteric hepatitis to necroinflammatory hepatitis (acute, recurrent, or chronic), cirrhosis, and carcinoma. (Loguercio & Federico, 2003).

HBV and hepatitis C virus (HCV) cause severe antioxidant depletion, and elevated levels of peroxidation products secondarily affect immune cells. HCV infection is characterized by a systemic oxidative stress that is most likely caused by a combination of chronic inflammation, iron overload, liver damage, and proteins encoded by HCV. The increased generation of reactive oxygen and nitrogen species, together with the decreased antioxidant defense, promotes the development and progression of hepatic and extrahepatic complications of HCV infection. Although both HCV and HBV cause hepatitis, HCV appears to be particularly potent at inducing oxidative stress, suggesting there are oxidative stress-inducing mechanisms that are unique to this virus. (Esrefoglu, 2012)

Immunohistochemical analyses in biopsies from patients with acute hepatitis demonstrated the expression of vascular cell adhesion molecules ICAM-1, ELAM-1, and VCAM-1 and T-cell homing receptor in sinusoids and areas of parenchymal necrosis. This supports the understanding of cytokine-induced upregulation of adhesiveness and recruitment of cytotoxic CD8 lymphocytes, with subsequent T-cell mediated cell death through the release of cytotoxic substances such as perforin and proteases (granzymes) or the induction of apoptosis via the FAS/Apo-1/CD 95 receptor system and mitochondrial dysfunction. Viral infection promotes apoptosis (in human liver diseases Councilman bodies are the expression of apoptosis). By this way the virus can inhibit or reduce the host immune response and therefore allow viral replication and propagation. (Loguercio & Federico, 2003).

X protein of HBV and HCV core regulates apoptosis through TNF- α, TGF- ß, IFN- γ, and IL-2 pathways; these cytokines also affect the progression of liver damage to chronicity.

On the contrary, the immune-mediated response of Th0/Th1 cytokines, such as IL-4 and IL-10, protects from the persistence of viruses and the appearance of fibrosis.

In vitro, the adhesion of HBV antigen depends on oxidative stress; the intracellular pathways that inhibit HBV gene expression and replication are mediated by IFN-γ and TNF- α, which also activate the post-transcriptional degradation of viral RNA in the nucleus. Both HCV and HBV are able to induce, via IFN- γ, hepatic iNOS, which mediates cellular damage through the production of TNF-α and IL- ß (Loguercio & Federico, 2003).

Second part

Experimental part

Materials & Methods

Materials and Methods

I.1. Patients and reagents

I .1.1. Study period

The period of our study is 6 Months, (from Decembre 2020 to May 2021) at the Infectious Diseases service of BEN AMOR DJILANI hospital (El Oued) and at the laboratory of Faculty of Natural Sciences and Life at the University of Echahid Hamma Lakhdar El-Oued.

I.1.2. Epidemiological study

The hepatitis reports of 1798 patients from hospital of Ben Amor Djilani hospital El-Oued were collected and information such as the patient‘s name, age, sex, type of hepatitis, region of patients . The data was compiled to get the percentage distribution and graphs were drawn for the individual data.

I.1.3. Biological study

For biological study, this study is carried out on 30 male volunteers, aged between 24-70years, were divided into two groups ; a group of 15 healthy control men aged 37.47±3.18 year, and 15 men has hepatitis aged 38.60±3.31 years .

Inclusion criteria

- Voluntary live in EL OUED region.
- Control group in good health, does not have any pathology.
- Voluntary was surfed from hepatitis.

Exclusion criteria

- Persons are suffering from other acute or chronic pathology.

I.1.4 Reagents

Ethylene diamine tetraacetic acid (EDTA), Hydrogen Peroxyde (H2O2), Hydrochloricacid (HCl) , Thiobarbituric acid (TBA) , Salicylic acid , Methanol, Tris, Trichloroacetic acid (TCA), Copper sulfate (CuSO 4) , Ascorbic acid, DTNB (5,5′-Dithiobis(2-nitrobenzoic acid)), Sodium chloride (NaCl) , Butylated hydroxytoluene (BHT) ,Phosphate-buffered (KH_2PO 4,K_2HPO 4), NBT, riboflavin.

I.2. Methods

I.2.1. Collection of data

We collect the risk and protective factors associated with hepatitis B.

I.2.1.1. Sample collection

About blood sampling for both groups is done morning fasting. It is performed in the vein of the end of the elbow. Blood samples is collected in three tubes. Dry tubes are centrifuged at 2500 rpm for 5 minutes, then obtained the serum to achieve the dosage of oxidative stress (MDA, GSH, SOD, and ORAC) parameters.

The anticoagulant tube (EDTA) is mixed well and then assays the hematological parameters.

The anticoagulant tube (Heparin) are centrifuged at 2000 rpm for 5 minutes , then recover the plasma to realize the dosage of biochemistry parameter: total bilirubin , direct biliribin , Aspartate aminotransferase (AST), Alanine aminotransferase (ALT) and alkaline phosphatase activity (AP) , and uric acid (U.A).

I.2.2. Method of Hematological analysis

Hematological analysis (FNS) is performed by the hematology Auto analyzer.

I.2.3. Biochemical parameters assay

Total bilirubin and uric acid Were determined by Auto analysis (BIOLIS24j) use commercial kits from Spinreact, (total bilirubin-20131, direct bilirubin 1001047,uric acid-1002011, Aspartate aminotransferase - 92025, Alanine aminotransferase -92027 , alkalin phosphatase-53123.

I.2.4. Method of estimating oxidative stress parameters

I.2.4.1. Malondialdehyde assay

MDA was measured according to the method described by (Yagi, 1976). Thiobarbituric acid 0.67% (w/v) was added to aliquots of the sample previously precipitated with 10% trichloroacetic acid (w/v). Then the mixture was centrifuged, and the supernatant was heated (100°C) for 15 min in a boiling water bath. Then cool in a cold water bath for 30 minutes, leaving the tubes open to allow evacuation of the gases formed during the reaction and the absorbance was measured at 532 nm using a spectrophotometer.

The concentration of TBARS was determined using the molecular extinction coefficient of MDA (a=1.53 105 M-1.Cm-1.The results were expressed in µmol / l

MDA (µmol/mg of HGB) = (Do échantillon/1.53 x 10^5) /mg of HGB

I.2.4.2.Determination of Reduced glutathione level

The determination of the reduced glutathione concentration by measuring the optical density results from the formation of 2-nitro-5-mercocapturic acid from the reduction of dithio-bis-2-nitrobenzoic acid, which is called reagent of Ellman with SH groupings exist in GSH briefly, 800 µL of homogenate are added to 200 µL of salicylic acid (0.25) and centrifuge at 1000 rpm for 5 minutes. 500 ml of supernatant are then mixed with 1000 µl of tris buffer (tris 0.4 mol, 0.02 molNaCl pH = 8.9) and 25 µL of DTNB (0.01 mol.L-1). After 5 minutes of incubation, the absorbance is read at 412 nm (Weakbeker& Cory, 1988).

$$GSH(nM/Mg\ of\ HGB) = \frac{DO \times 1 \times 1.525}{13133 \times 0.8 \times 0.5 \times mg\ of\ HGB} \times d$$

13133: Absorption constant of SH groups at 412 nm.

OD: The absorbance reader by the spectrophotometer.

521.1ml: Total volume of blend.

521ml: Volume of solution float.

1: Volume of protein mixture.

0.8 ml: Volume of homogeneous solution without protein exists in 1ml.

GSH: Concentration of glutathione.

I.2.4.3. Determination of catalase activity:

The catalase activity consists in measuring the catalase-induced H2O2disappearance contained in the sample by measuring the absorbance of H2O2 at 560 nm using a UV / visible spectrophotometer. Briefly in test tubes, mix 1 ml of phosphate buffer (0.1 mHg, 0.1M, pH7.2), 0.975 ml of freshly prepared H2O2 (0.091M) and 0.025 ml of the enzyme source (serum). Absorption read at 560 nm every minute for 2 minutes.

$$\mathbf{CAT(UI\ /g)} = \frac{\mathbf{(2{,}3033\ /T)}}{\boldsymbol{g\ of\ HGB}} \times \mathbf{(\log A1 / \log A2)}$$

I.2.4.4. Determination of superoxide dismutase activity assay

The assay method of SOD activity using the NBT by the superoxide anion ($O2^{\cdot}$), is used as a basis for detecting of presence of SOD by measuring the spectrophotometrically absorbance at 560 nm (Beauchamp & Fridovich,1971).

Table 04 : superoxide dismutase activity assay.

Collect in tubes	Blank	Sample
EDTA-Met 0.1mM EDTA-13mM Met	1000µL	1000µL
Phosphate buffer (50Mm)	892.2µL	892.2µL
Sample	0	50
Phosphate buffer	1000µL	950µL
NBT (75µM)	85.2µL	85.2µL
Riboflavin (2µM)	22.6µL	22.6µL

Expression of results:

$$\mathbf{SOD}\left(\frac{\mathbf{U}}{\mathbf{g\ of\ HGB}}\right) = \frac{\boldsymbol{OD\ blanc} - \mathbf{OD\ sample}}{\boldsymbol{OD\ blanc}} \times \mathbf{100}$$

I.2.4.5. Determination of antioxidant power

a. Principle

The total antioxidant power of the serum,its capacity to absorb free oxygen radicals (ORAC: Oxygen Radical Absorbance Capacity), is estimated by the ability of red blood cells to resist free radical-induced hemolysis in vitro in the presence of serum according to the method of (Oyaizu, 1986). This method is based on the time-dependent monitoring of red blood cell hemolysis induced by a free radical generator.

b. Treatment of red blood cells

Centrifuge donor blood at 2000 rpm for 10 min and remove plasma.

Wash gently 1 volume of the pellet with 2 volumes of physiological saline (without lysing the RBCs), then centrifuge again at 2000 rpm for 5 min.

c. Operating mode

Control tube

Add 1 ml of RC: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30) and 2 ml of physiological saline, then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

Repeat this operation every 10 minutes for 1 hour.

Standard tube

To 1 ml of GR are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30) and 2 ml of physiological saline, and 20 µl of vitamin C (400 µM) and then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

Repeat this operation every 10 minutes for 1 hour.

Test tube

To 1 ml of RC are added: 20 µl of CuSO4 (2 mM), 20 µl of H2O2 (30) and 2 ml of physiological saline, and 20 µl of serum (400 µM) and then stir gently. Incubate for 5 min at room temperature, centrifuge for 5 min at 2000 rpm.

Read the OD at 450 nm from the supernatant and put it back into the tube and stir gently.

Repeat this operation every 10 min for 1 hour (t0, t10, t20, t30, t40, t50, t60, and average the latter:

$\Sigma DO = \Sigma (t0, t10, t20, t30, t40, t50, t60) / 7$

To calculate the total antioxidant power using two methods.

Calculate method

$$\textbf{ORAC (UI)} = \frac{\sum(\textbf{DO blanc} - \textbf{DO échantillon})\,\Delta t}{\sum(\textbf{DO blanc} - \textbf{DO étalon})\,\Delta t}$$

I.3.Statistical analysis

Statistical analysis is performed by the SPSSV20.0 software results comparisons were carried out by using the Student T test to compare means among the groups, Correlation analysis was carried out using Pearson Correlation test and regression analysis was used for other analysis and statistical data. Differences were considered statically significant at $p < 0.05$.

Results

I. Result

II.1. Epidemiological study of hepatitis patients

In this study, the number of hospital hepatitis patient was about 1798 patients registered in EL OUED.

II.1.1. Distribution of the hospital hepatitis patients by sex

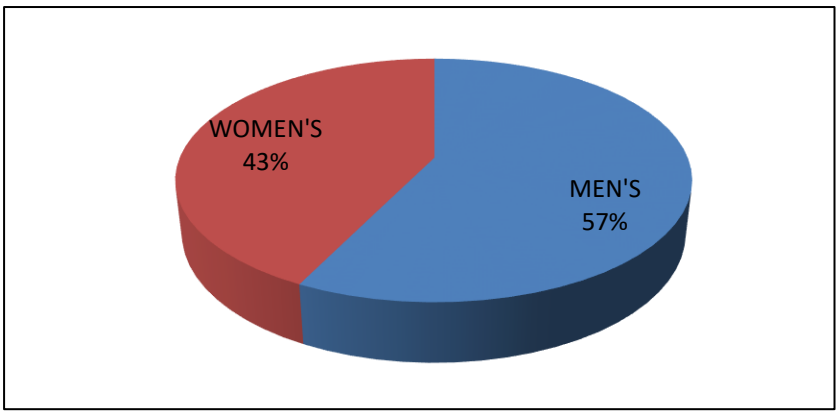


Figure 22: Distribution of the hepatitis patients among men's and women's.

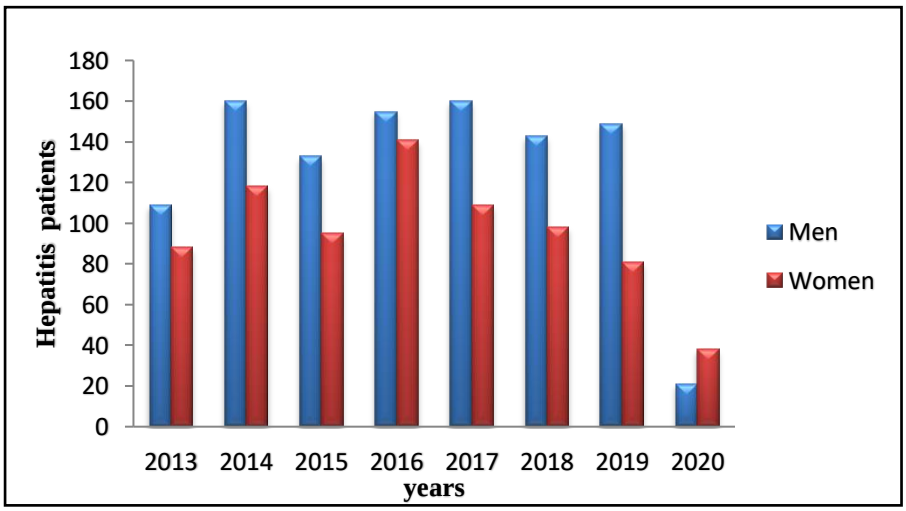


Figure 23: Distribution of the hepatitis patients among men's and women's.

A total of 1798 cases of hepatitis patients were analyzed. Based on data collected between 2013-2020 from Infectious Diseases service of BEN AMOR DJILANI hospital, it's were found that man's accounted for *57.29*% of the hepatitis population and women's accounted for *42.71*% (figure 22, 23).

II.1 .2. Distribution of the hospital hepatitis patients according to the age group

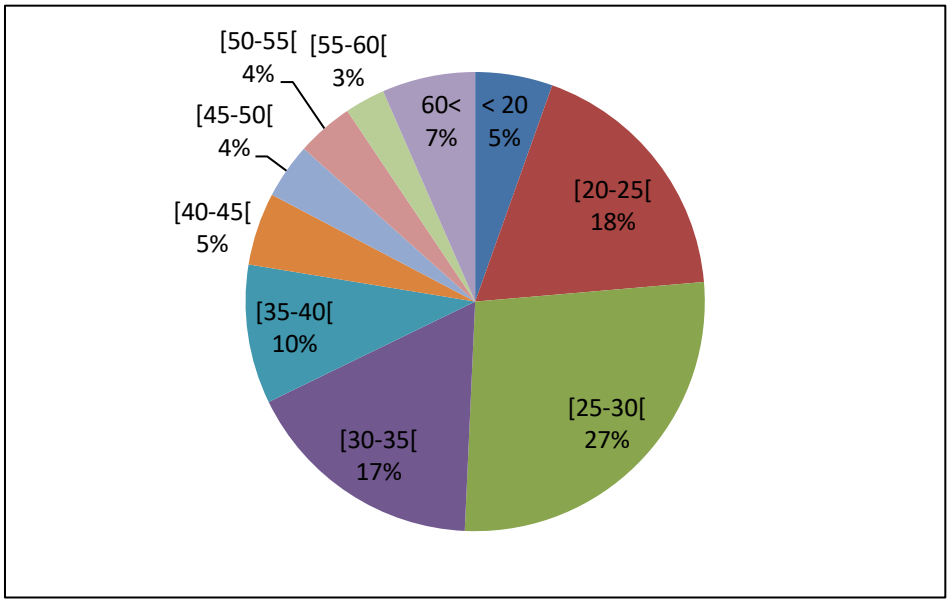


Figure 24 : Distribution of hepatitis patients according to the age groups in El Oued Region.

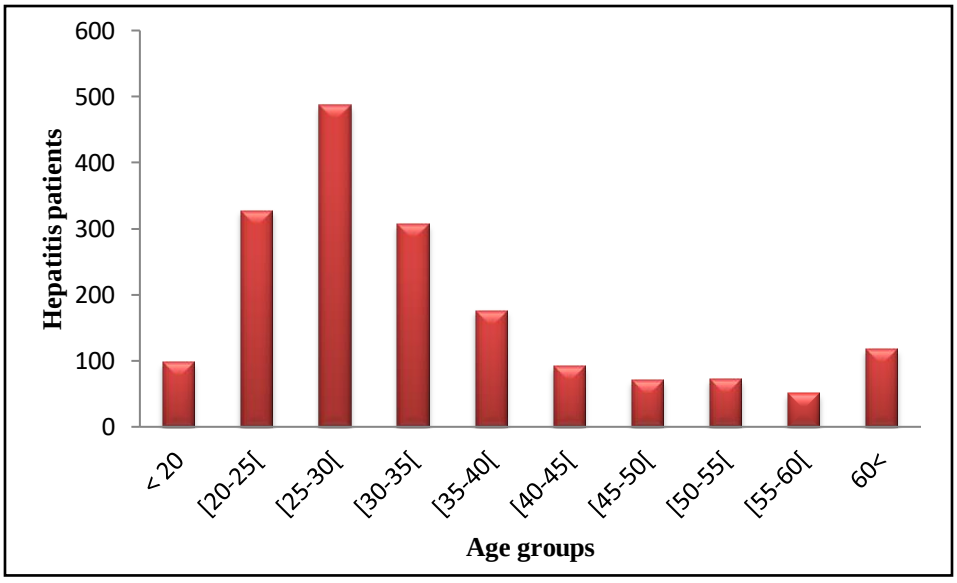


Figure 25: Distribution of hepatitis patients according to the Age groups in El Oued Region.

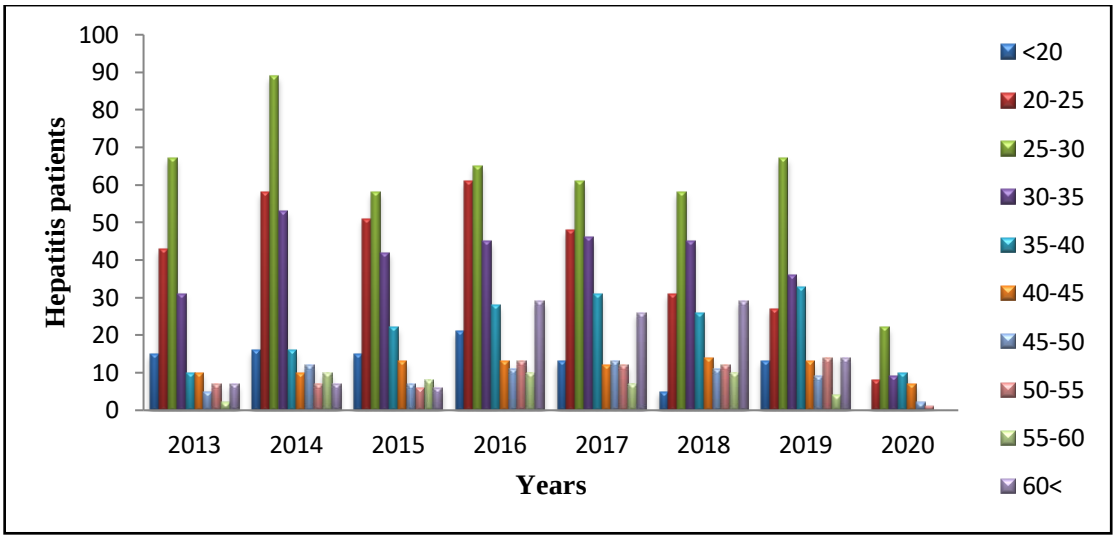


Figure 26: Distribution of the hospital hepatitis patients according to the age group in each year.

It was found that there were low hepatitis patients (5%) between the age groups 0-20 years of age. 18% of the people between 20-25 years, 27% of the people between ages 25-30 years, 17% of the people between ages 30-35, 10% of the people between ages 35-40, 5% of the people between ages 40-45, 4% of the people between ages 45-50, 4% of the people between ages 50-55, 3% of the people between ages 55-60, 7% of people have more than 60 years were found to be affected by hepatitis in El Oued population (figure 24, 25, 26).

II.1.3. Distribution of the hospital hepatitis patients according to the hepatitis type

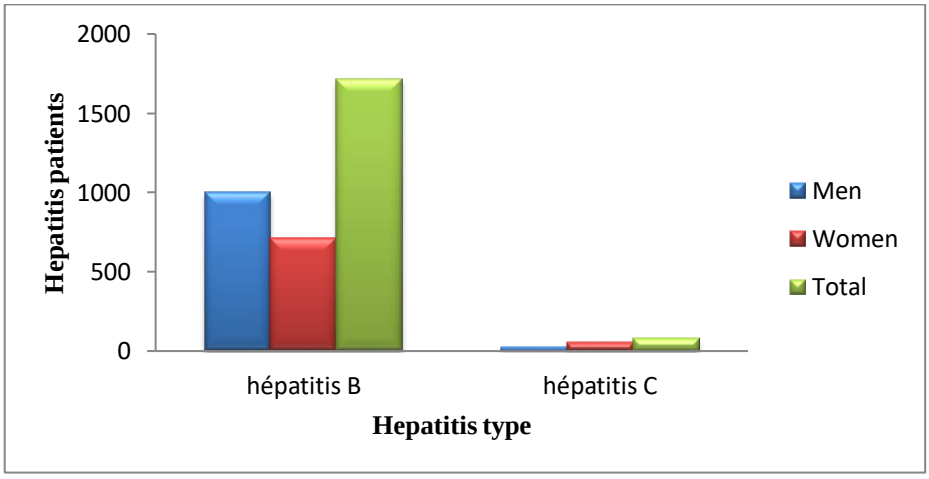


Figure 27: Total distribution and according to the sex of hepatitis patients in each type of hepatitis.

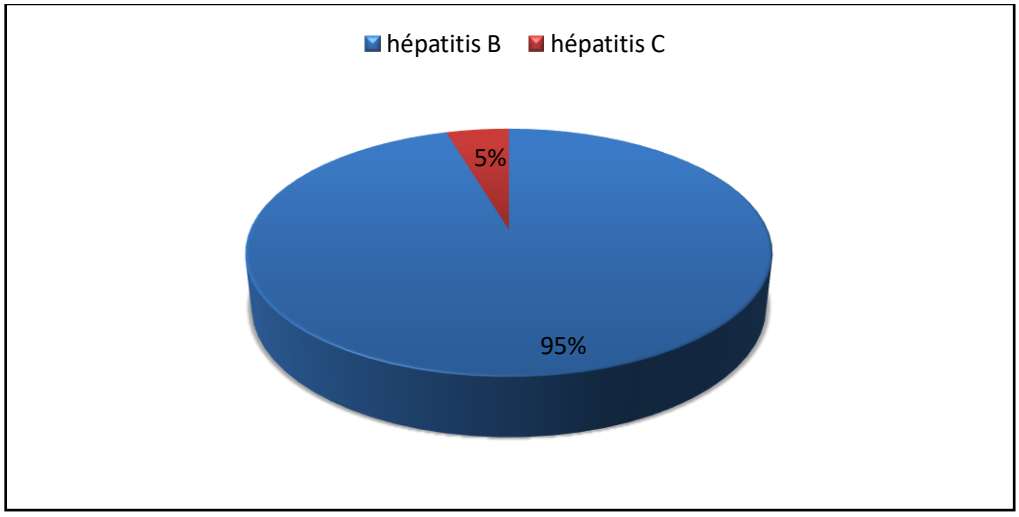


Figure 28: Distribution of hepatitis patients according to the hepatitis type.

The most common type of hepatitis in this study was found to hepatitis B type with a distribution of 95% when compared to hepatitis C with 5% (Figure 27, 28).

II.1.4. Distribution of the hospital hepatitis patients according to the region

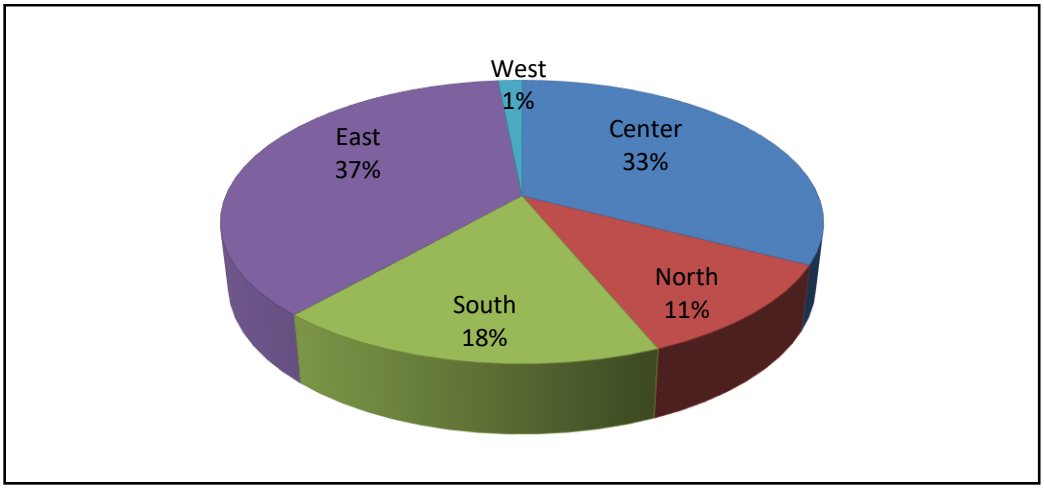


Figure 29: Distribution of hepatitis patients by regions of the state of El Oued.

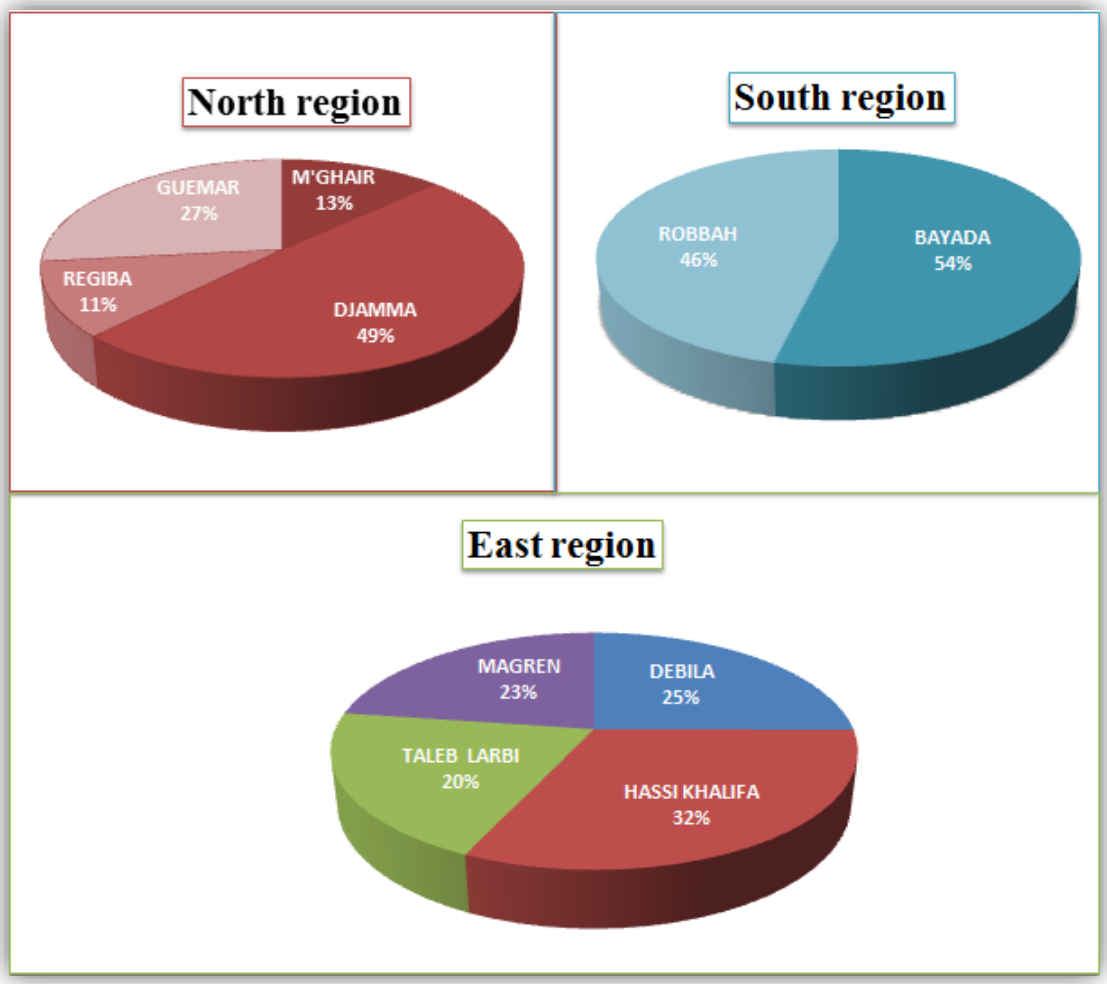


Figure 30: Distribution of hepatitis patients in the different Dairas in each region. (west and center)

It was found in this study that 31,15% of the hepatitis patients are from the central region of the state of El Oued. It was found also that 10,62% the patients are from the North region, 16,91% of the patients are from South region, 35,26% of the patients are from East region and 1,44% of the patients are from West region of El Oued area (figure 29).

The central region is known for its large population density and it consists of the Daira of El Oued. the northern region consists of the Dairas of El M'ghair, Geumar, Reugiba and Djamaa, it is known as a large population density. The southern region has a medium population density and include the Dairas of Robbah and Bayada. The eastern region is known to have a large population density, including the Dairas of Taleb Larbi, Debila, Hassi Khalifa and Magrane. The western region is dominated by the deserts and consists of the Daira of Mih ounsa (figure 30).

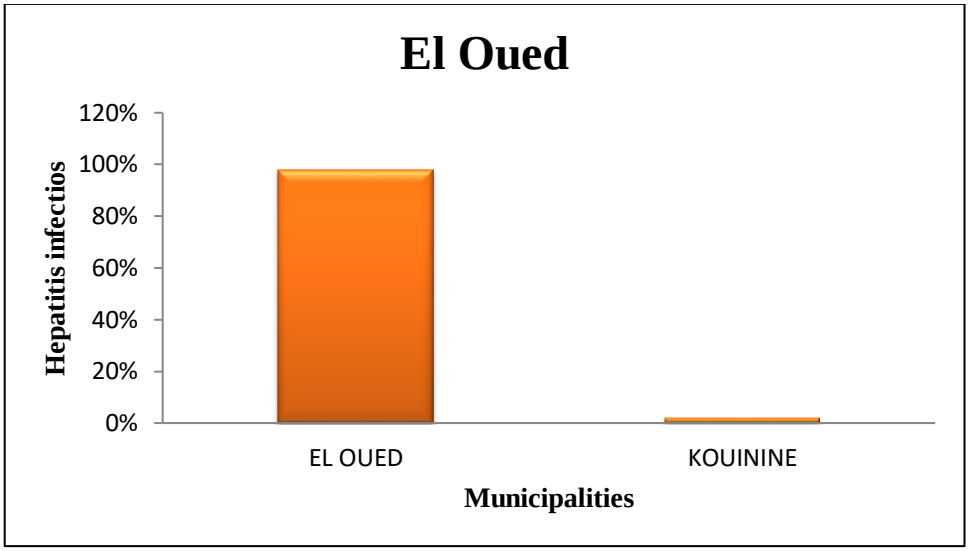


Figure 31: Distribution of the hepatitis patients in the municipalities of the Daira of El Oued in the central region.

The largest number of hepatitis patients was found in the eastern region, followed by the central region, the south region, the north region and the western region with the lowest number of hepatitis patiets in the state of El Oued.

About the central region, the majority of hepatitis patients is from the municipality of El Oued and represented 98% of total cases and 2% from Quinin (figure 31).

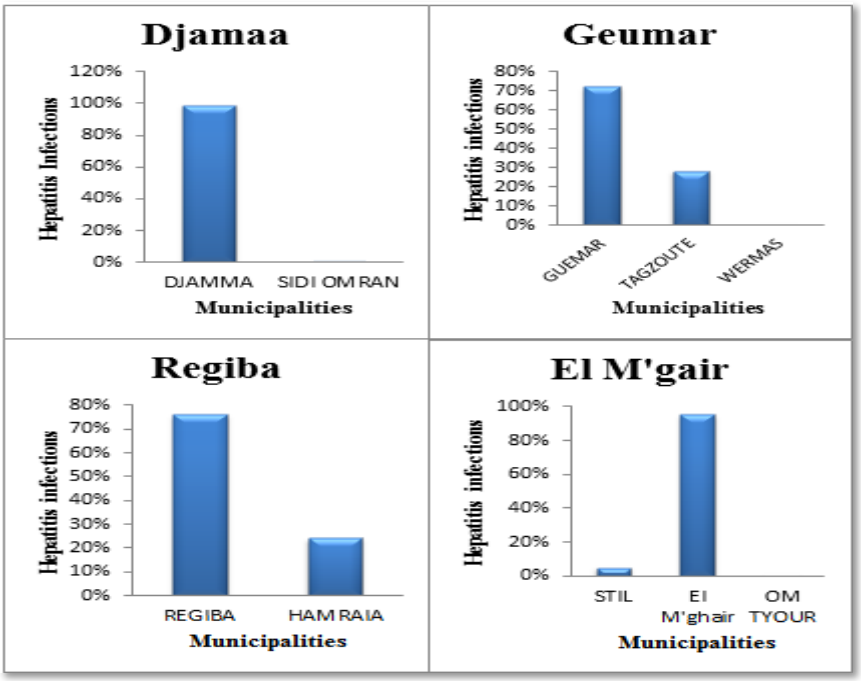


Figure 32: Distribution of the hepatitis patients in the different municipalities of the Dairas of the North region.

In the northern region, Djamaa has the largest number of hepatitis patients with 44% of a total case in this region so 99% of them are residing in Djamaa municipality and just 1% are residing in Sidi Omrane municipality. In the second place come Geumar with a total of 24% of hepatitis patients distributed between Geumar municipality by 72% and Taghzout municipality by 28%, with complete absence of hepatitis patients in the municipality of Wermas. In the Daira of Regiba, hepatitis patients represent 20% of a total case in the northern region, with most of them are located in Regiba municipality (76%) and the rest are residing in Hamraya municipality (24%). El M'ghair has the lowest number of hepatitis patients (12 %) in the northern region of the state of El-Oued, 95% of them are located in El M'ghair municipality and the 5% resting are located in Stil municipality with no hepatitis patients found in Oum Tyour municipality (figure 32).

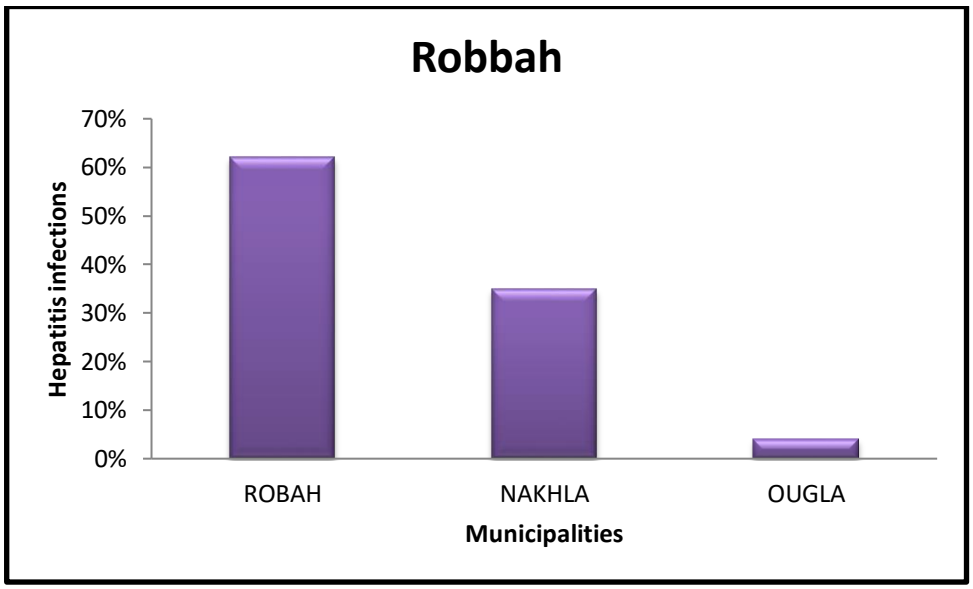


Figure 33: Distribution of the hepatitis patients in the municipalities of the Daira of Robbah in the South region.

With regard to the southern region, we find that the hepatitis patients are distributed over two Dairas, Bayada and Robbah, and they are located in Bayada (54%) more than in Robbah (46%). In the Daira of Bayada, all the hepatitis patients are located in the only municipality of this Daira, Bayada municipality. In Robbah, hepatitis patients are divided into three municipalities, majority of them are residing in Robbah municipality and represent 62%, patients of Nakhla municipality represent 35%, Ogla municipality has the lowest number of hepatitis patients in the southern region of the state of El-Oued with 4% (figure 33).

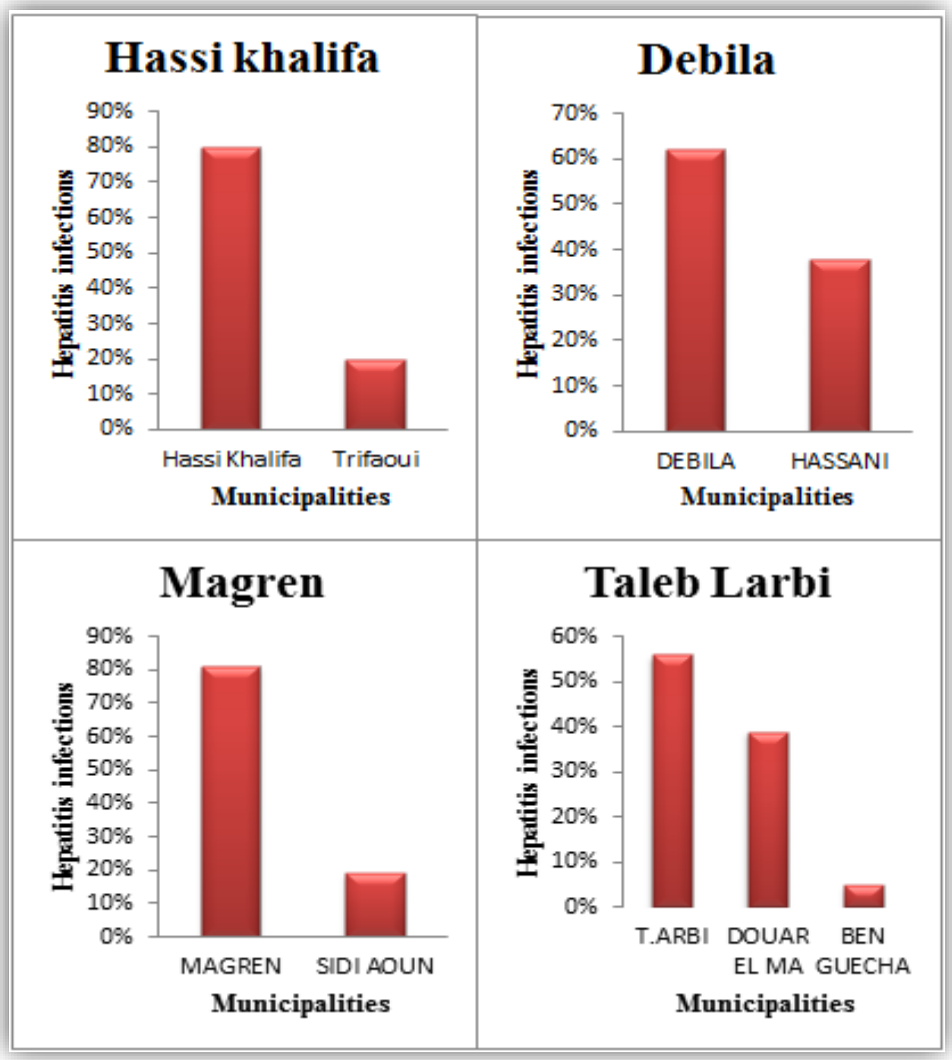


Figure 34: Distribution of the hepatitis patients in the different municipalities of the Dairas of the East region.

About the eastern region, the largest distribution of hepatitis patients was in Hassi Khalifa with 32%, in this Daira, most of hepatitis patients are concentrated in Hassi Khalifa municipality with 80% and the 20% resting are located in Trifaoui municipality. Dabila is the second largest distribution center of hepatitis patients with 25% of a total casese in the eastern region, 62% of them are residing in Debila municipality and 38% are residing in Hassani Abd Elkarim. After it come the Daira of Magren with 23% of a total cases in this region with 81% of them are located in Magren municipality and 19% in Sidi Aoun. And at least Taleb Larbi with 20% of hepatitis patients divided into three municipalities, Taleb Larbi (56%), Douar Lmaa (39%) and Ben Geucha (5%) (figure 34).

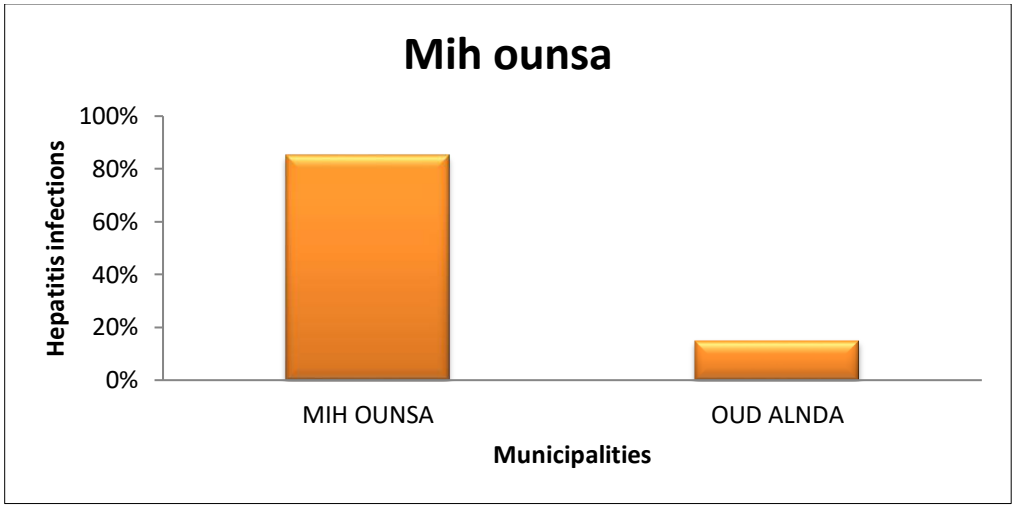


Figure 35: Distribution of the hepatitis patients in the municipalities of the Daira of Mih ounsa in the West region.

About the Western region, the majority of hepatitis patients are from the municipality of Mih Ounsa and represented 95% of a total cases and 15% are from Oued Alanda (figure 35).

II.2.Study of biological markers and predictive factors

II.2.1. Description of study population

For biological study, this study is carried out on 30 male volunteers, were divided into two groups ; a group of 15 healthy control men, and 15 men has hepatitis, the average age of the controls are (25-65) , Ranging weights shown (65-80) , They have different blood groups (A+;AB+;O+;B+) and they live in EL OUED . The average age of the patients are (25-70), Ranging weights shown (65-90) , They have different blood groups (A+;O+) and they live in EL OUED.

II.2.2.Hematological markers

The results of the hematological analysis for control and hepatitis patient are illustrated in table 05. the result show that the leukocytes lineage (WBC, MONO, NEUT) are significantly increased ($P < 0.01$) in the patients group as compared to the control group, LYM level is shown that no significant differences ($P > 0.05$).

In erythrocyte line, (HGB, RBC, and HCT) are significantly decreased (P< 0.05) while MCV is significantly increased (P < 0.001) in patients group as compared to the control group.

the Platelet line (PDW, MPV and PLT) is significant increase (P < 0.05 and P < 0.001) respectively in patient group as compared to the control group. PCT level is shown that no significant differences (P > 0.05).

Table 05: Hematological parameters levels in control and hepatitis patient groups.

		Control group	Hepatitis group	P- Value
Erythrocyte line	**WBC (10*9/L)**	6.542 ± 0,397	8.382 ± 0.636	**0,000**
	LYM (10*9/L)	3.28 ± 0,18	3.15 ± 0.24	0,463
	MONO (10*9/L)	1.23 ± 0,11	1.64 ± 0.19	**0,006**
	NEUT (10*9/L)	2.3 ± 0,2	4.12 ± 0.27	**0,000**
Leukocyte line	**RBC (10*12/L)**	4.87 ± 0,09	4.47 ± 0.22	**0,017**
	HGB (9/DL)	14.70 ± 0,25	13.57 ± 0.75	**0,040**
	HCT (%)	42.16 ± 0,69	39.32 ± 1.97	**0,048**
	MCV (FL)	84.79 ± 1,54	89.16 ± 0.7	**0,000**
Platelet line	**PLT (10*9/L)**	175.5 ± 5,57	211.93 ± 6.58	**0,000**
	PCT (%)	21.61 ± 1,98	22.23 ± 0.87	0,312
	MPV (FL)	10.12 ± 0,09	10.8 ± 0.43	**0,032**
	PDW (%)	11.12 ± 0,22	11.5 ± 0.27	0,059

II.2.3.Biochemical markers

Concerning biochemical markers**,** our result show in the table 06 demonstrated that a significant increase in total bilirubin, direct bilirubin level, AST, ALT and alkaline phosphatase (P < 0.001) and significant decrease in uric acid (P < 0.001) in the patients group as compared to the control group.

Table 06: Biochemical parameters levels in control and hepatitis patient groups.

Parameters	Control group	Hepatitis group	P Value
Serum AST (ul/l)	16.32 ± 1.54	20.42 ± 1.53	**0,001**
Serum ALT (ul/l)	15.12 ± 0.83	19.09 ± 1.88	**0,005**
Serum ALP (ul/l)	203.2 ± 12.2	369.7 ± 34.6	**0,000**
Serum Uric acid (umol/L)	50.91 ± 1.06	36.34 ± 2.57	**0,000**
Total Bilirubine (mg/l)	4.36 ± 0.24	6.31 ± 0.65	**0,000**
Direct Bilirubine (mg/l)	1.37 ± 0.14	2.81 ± 0.64	**0,003**

II.2.4.Oxidative stress markers

The analysis of blood oxidative stress parameters in control and hepatits patient are shown in table 07. For man our result explained a significant increase ($P < 0.001$) of serum MDA level, SOD, catalase and ORAC activities, also a significant decrease ($P < 0.001$) of serum GSH in patient group compared to control group.

Table 07: Oxidative stress parameters in the blood of control and hepatitis patient.

Parameters	Control groups	Hepatitis groups	P Value
Serum MDA (nM/g Hb)	3.509 ± 0.472	12.03 ± 1.14	**0,000**
Serum GSH (nM/g Hb)	2.595 ± 0.269	1,012± 0.231	**0,000**
Serum SOD (UI/g Hb)	1.67 ± 0.08	7.66 ± 2.13	**0,000**
Serum CAT (UI/g Hb)	0.01±0.0005	0.07±0.02	**0,000**
ORAC (UI/l)	0.5677±0.0890	0 .960±0.132	**0,000**

II.2.5. Predictive factors study

Our result explained that serum MDA, serum SOD , serum GSH, serum CATALASE and serum ORAC are shown in table 08 were a significant predictive factor ($P < 0.05$) with an important percentage of sensitivity (63,3 ; 54,5 ; 45,5 ; 81,8 ; 70 %) respectively, with AUC value (0.00 ; 0,058 ; 0,901 ; 0,074 ; 0,791) respectively and a high percentage of specificity in serum MDA, SOD and CAT (100 %), a medium percentage of specificity in serum ORAC (36,4 %) and lower percentage of specificity in serum GSH (9,1%)

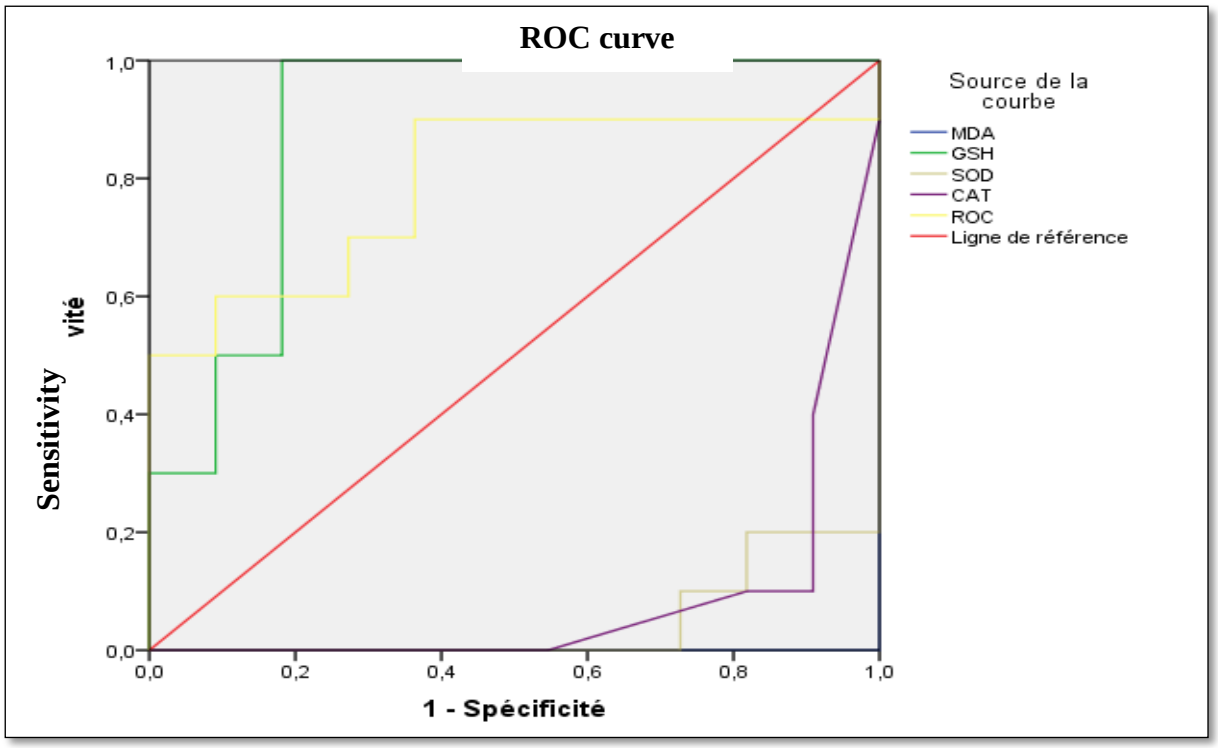


Figure 36 : ROC Curve for oxidative stress markers.

Specificity

Table 08: Sensitivity, specificity and AUC values of some oxidative stress markers.

variable(s)	Sensitivity (%)	Specificity (%)	AUC (%)	P- Value	CI 95%
Serum MDA	63,6	100	0,00	**0,000**	0,000-0,000
Serum SOD	54,5	100	0,058	**0,000**	0,000-0,148
Serum GSH	45,5	09,1	0,901	**0,001**	0,761-1,000
Serum CAT	81,8	100	0,074	**0,001**	0,000-0,192
Serum ORAC	70,0	36,4	0,791	**0 ,024**	0,580-1,000

II.2.6 Correlation between biological markers

II.2.6.1. Control group

The correlation results between oxidative stress parameters, Hematological parameters, and biochemistry markers for healthy controls are shown in figures 36, 37 and 38. we learned a positive correlation with P < 0,05 between MDA and both of PDW and ALP.

In other hand there was a negative correlation with P<0. 001 between (CAT / HGB). In addition, a negative correlation with P<0.01 was found between (GSH / HGB) and between CAT and all of MCV, MPV and HCT. a negative correlation with P<0.05 was found between GSH and both of RBC and HCT.

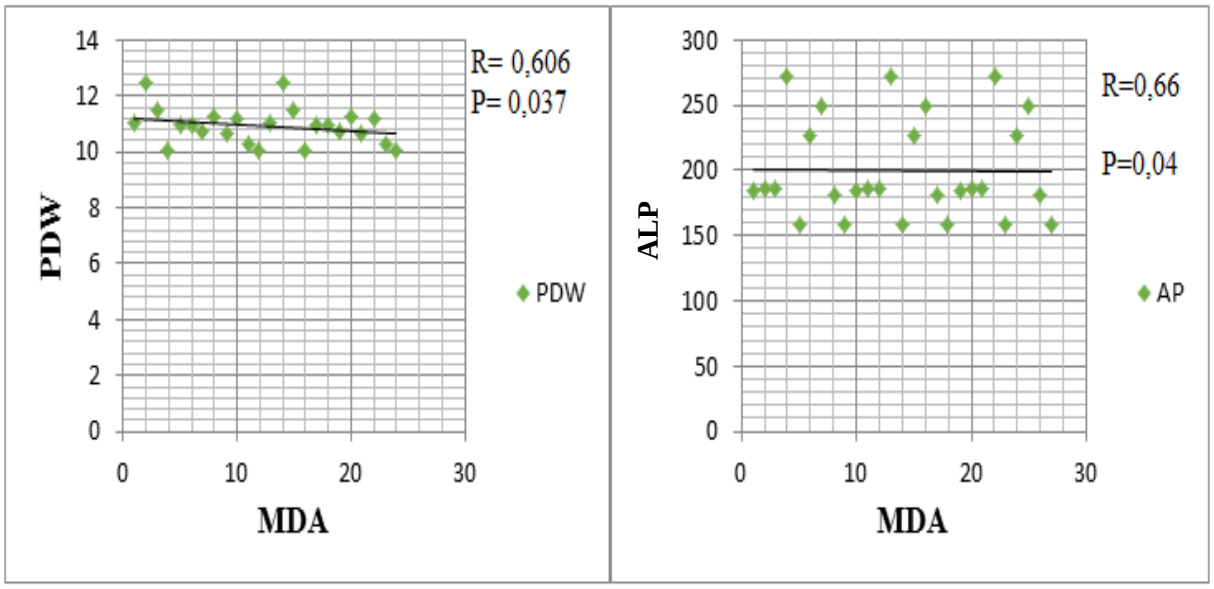


Figure 37: Correlation between biochemical/hematological markers and MDA for healthy controls.

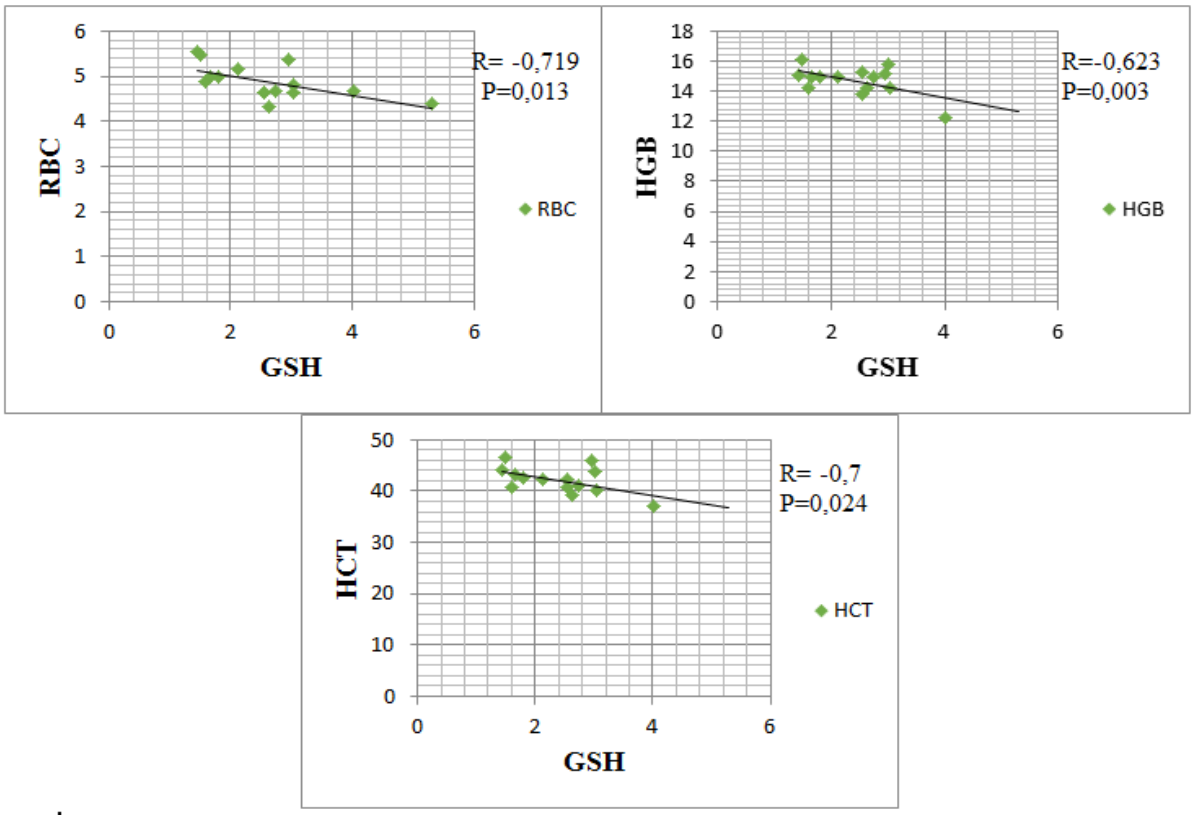


Figure 38: Correlation between biochemical/hematological markers and GSH for healthy controls.

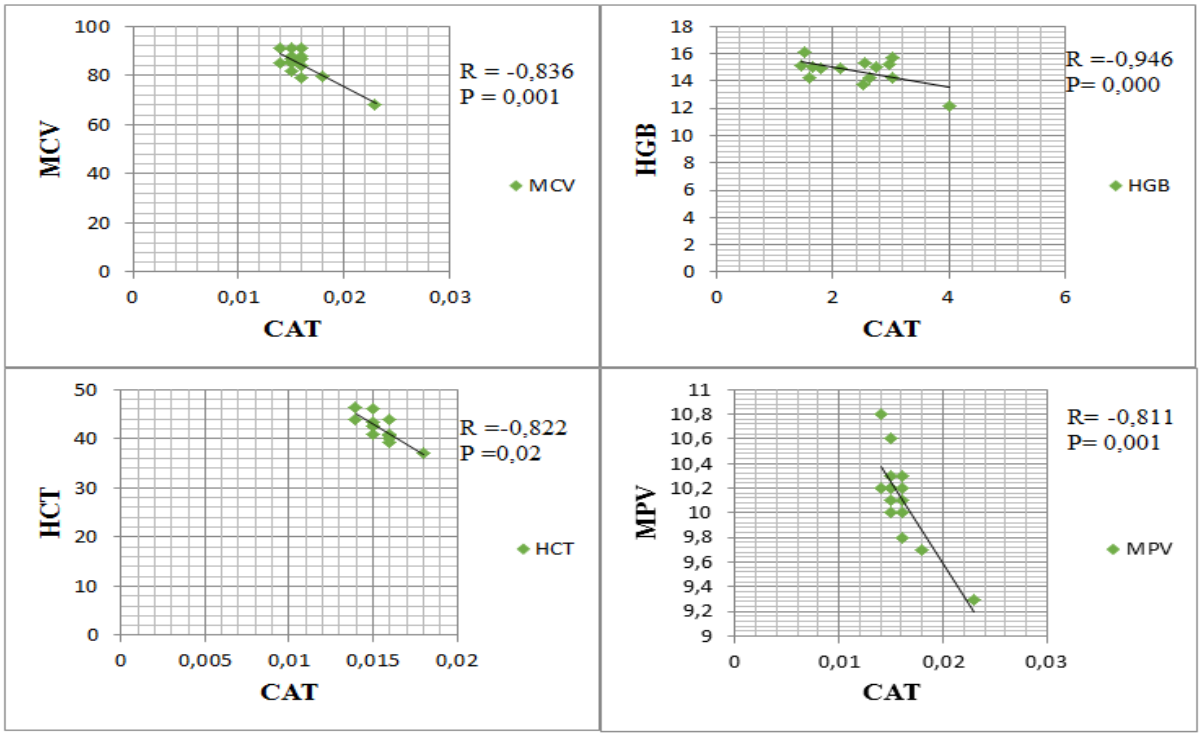


Figure 39: Correlation between biochemical/hematological markers and CAT for healthy controls.

II.2.6.2. Hepatitis group

The correlation results between oxidative stress parameters, Hematological parameters and biochemistry markers for hepatitis patients are shown in the figures 39, 40, 41 and 42**.** we learned a positive correlation with P < 0,01 between (MDA / PDW) and between GSH and both of MONO and U.A. In contrast, a positive correlation with P < 0,05 is found between (SOD / MPV), (GSH / WBC) and between CAT and both of RBC and MPV.

In other hand there was a negative correlation with P<0.001 between MDA and both of RBC and HGB. In addition, a negative correlation with P<0.01 was found between (GSH / U.A) and between CAT and both of HCT and ALP. As well, a negative correlation with P<0.05 was found between (MDA / U.A), (ORAC / NEUT) and between GSH and both of HCT and ALT. There was no correlation (P>0.05) between the rests of correlation test in patients groups.

Figure 40: Correlation between biochemical/hematological markers and MDA for hepatitis patients.

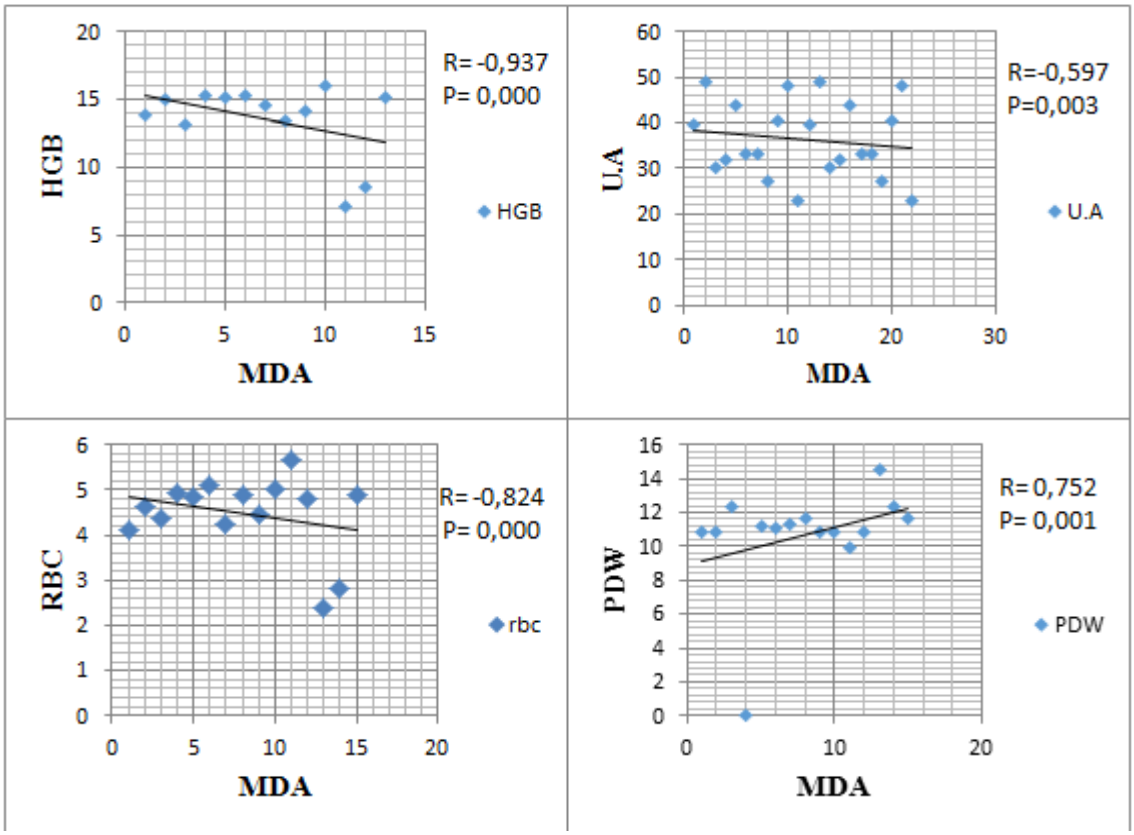


Figure 41 : Correlation between biochemical/hematological markers and CAT for hepatitis patients.

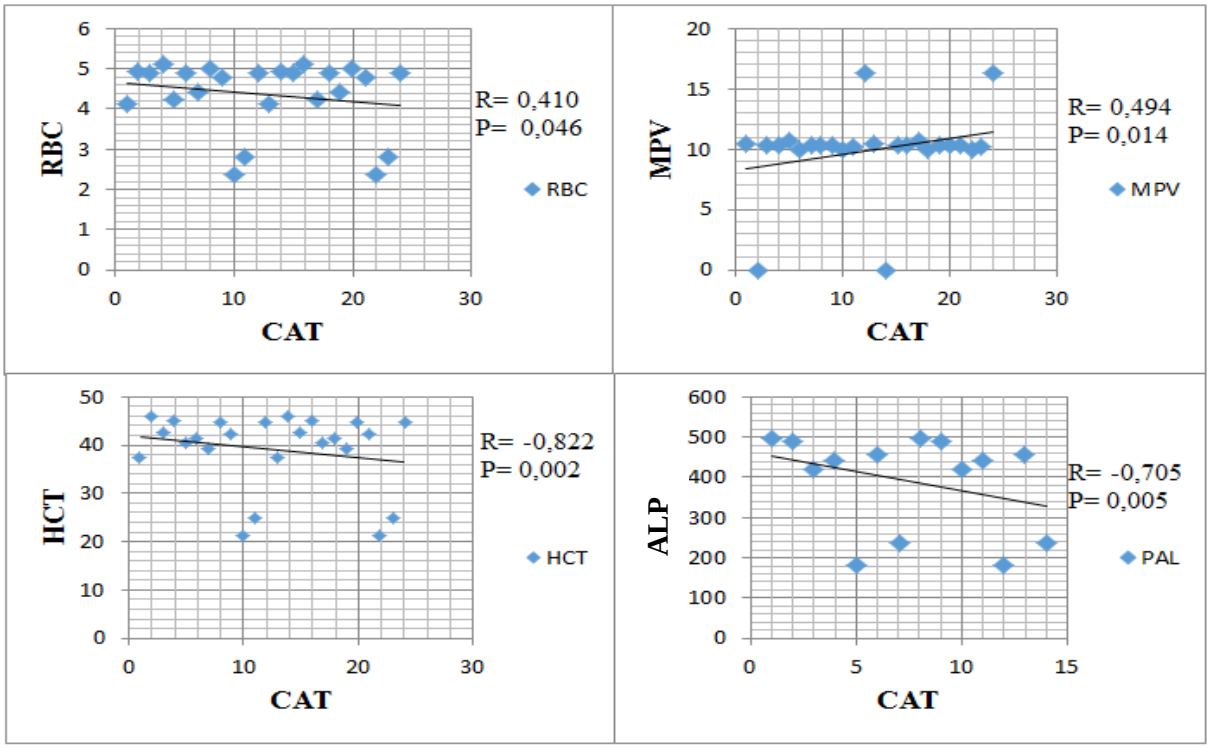


Figure 42: Correlation between biochemical/hematological markers and ORAC for hepatitis patients.

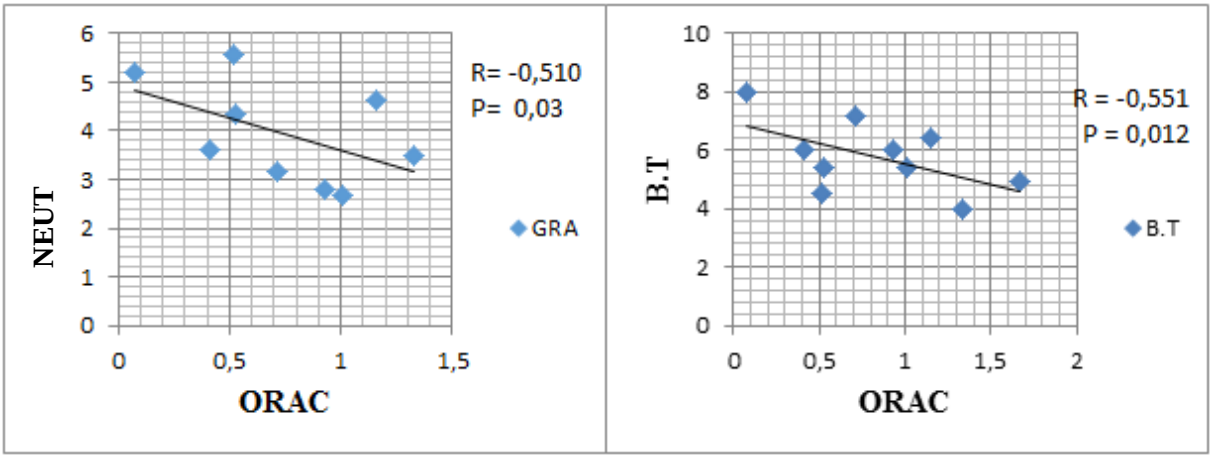


Figure 43 : Correlation between biochemical/hematological markers and GSH for hepatitis patients.

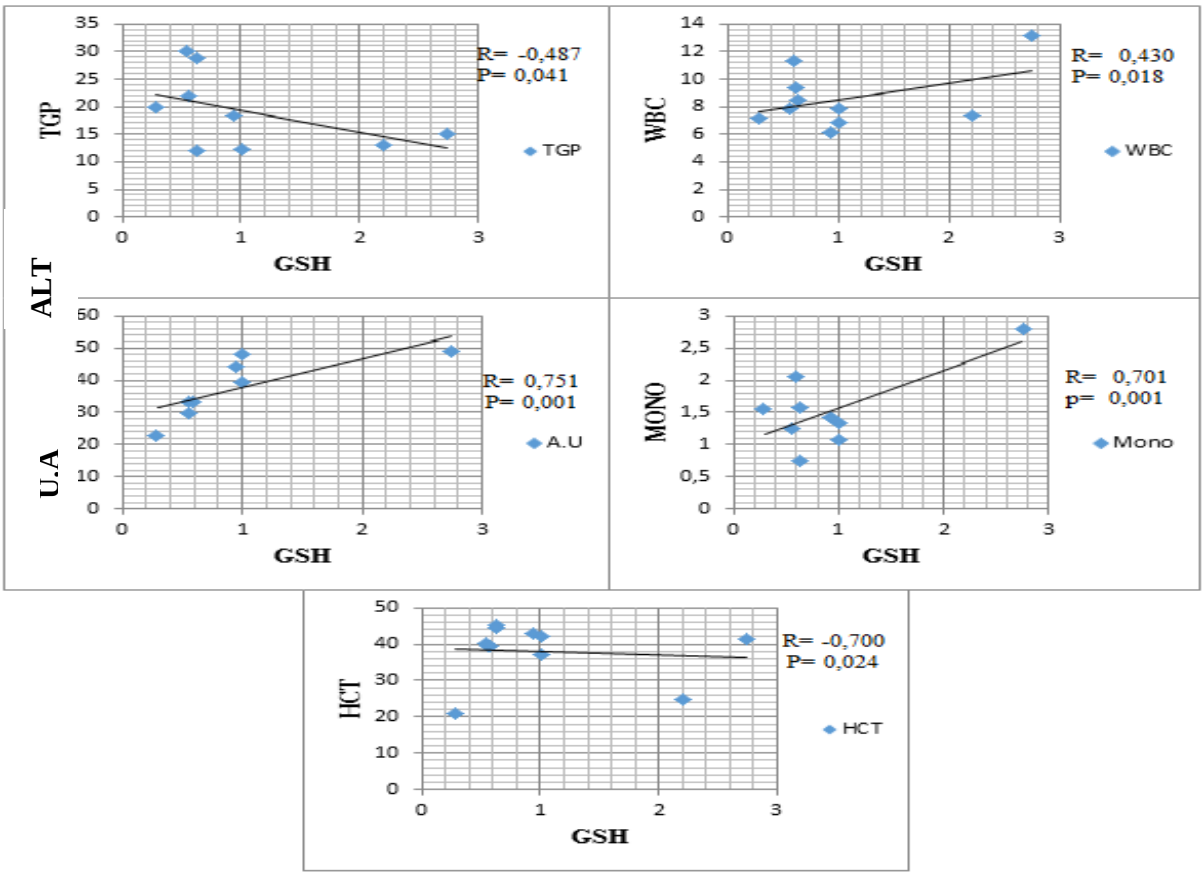
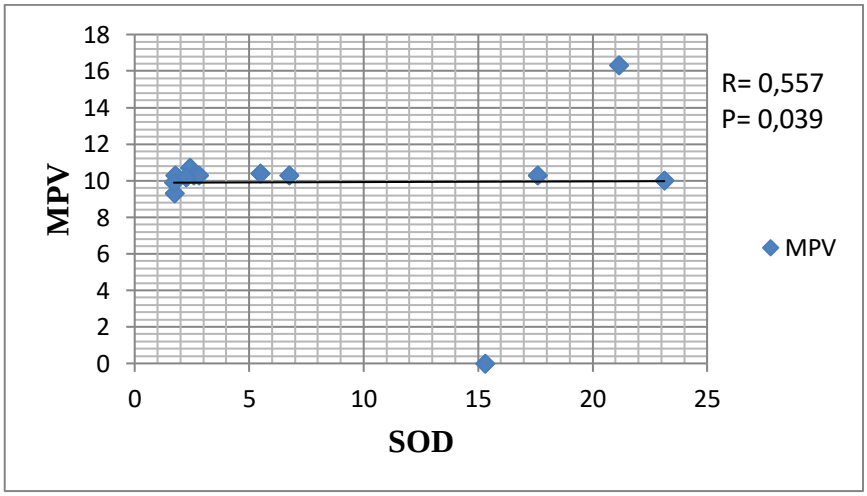


Figure 44 : Correlation between biochemical/hematological markers and SOD for hepatitis patients.



II.2.7. Biological risk factor Study

Odds Ratio (OR) values for oxidative stress factors (Table 09) show that GSH, CAT and SOD are shown to be significant risk factors for the hepatitis (OR = 12,000 ; p = 0.032, OR=15,40 ; p=0.014 and OR = 9,75; p = 0.038) respectively.

Table 09: Comparison of the oxidative stress factors of hepatitis patients and control (N=30).

	CONTROL (%)		HEPATITS (%)		OR	CI 95%	*P-value*
	Positive	**Negative**	**Positive**	**Negative**			
GSH	54.54	45.45	9 .09	90.90	12.000	1.118-128.836	**0.032**
CAT	58.33	38.46	7.69	84.61	15.40	1.473-160.972	**0.014**
SOD	42.85	57.14	7.14	92.85	9.75	0.984-96 .56	**0.038**
ORAC	30	70	53.84	46.15	0.367	0.065-2 .087	0.237
MDA	41.66	58.33	8.33	91.66	7.857	0.752-82.128	0.077

Discussion

III. Discussion

III.1.Epidemiological study of hepatitis in EL-Oued region

In our epidemiological study, we found that, hepatitis occurs to be most commonly affecting the males when compared to the females. This result is in concurrence with another studies (Tsay et al., 2009 ; Wang et al., 2018 ; Kim, 2009) which found that the prevalence of serum HBV surface antigen (HBsAg) has been reported higher in men than in women.A similar studies conducted by (Farza et al., 1987) and (Breidbart et al., 1993) found that female HBV carriers have lower viral loads than male carriers .According to Baruch S et al (Saeeda & Mohiuddin, 2009), Females are more likely than males to produce anti-HBs in response to infection.

The innate immune response is the first line of defense against viruses and it is mediated by Toll-like receptors (TLRs), retinoic acid-inducible gene I-like receptors (RIG-I) and nucleotide oligomerization domain-like receptors (NOD-like receptors). These, named pattern recognition receptors (PRRs), recognize viral components (such as DNA, dsRNA, ssRNA, and viral proteins) and activate production of type 1 interferon (IFN) and inflammatory cytokines (IL-1, TNFs). In rodents and in humans expression of TLRs (such as TLR7) as well as number of monocytes, macrophages and dendritic cells, that are innate immune response players, have been reported to be significantly higher in females than in males, thus accomplishing the more intense inflammatory responses in female subjects than in males.once a viral infection is established, the activation, by the Antigen Presenting Cells (APCs), of adaptive immune responses and of B cells, with subsequent rise of the antibodies specific for viral antigens, in most cases is greater in female animals and humans compared to males. In addition, females have higher number of $CD4^{+}$T cells than males, that induces a greater number of T cells activated by viral antigens engagement of the T cell receptor ; moreover, stronger cytotoxic T cell activity along with overexpression of antiviral and pro-inflammatory genes, many of which have estrogen response elements in their promoters, have been reported in women.

Based on this, it is deductible that female are less prone than males to be virus infected, due to their more effective antiviral immune defenses, but more frequently they develop more severe symptoms, due to the more intense inflammatory responses.

Furthermore, the presence of different sex hormones, which circulate at different levels in males and females, makes sense of the fact that the immune responses are differentially modulated in individuals of different sexes. The immunological dimorphism between sexes, besides being shaped by the individual genetic background, is mostly regulated by sex steroids hormones, particularly by estrogens, progesterone and androgens, that affect function of the immune cells. Due to the expression of the sex hormone receptors on immune cells, including lymphocytes, monocytes and dendritic cells, the interaction of sex hormones and immune cells affects release of cytokines and chemokines, which determine differentiation, maturation and proliferation of the immune cells.

Actually, several studies have indicated that androgens exert an overall inhibitory effect on differentiation of Th1 arm of the immune system, with consequent reduced production of IFN-γ that may explain the enhanced susceptibility to viral infections in males than in females. (Ruggieri et al., 2018)

Concerning the distribution of hepatitis according the age group , our study demonstrated that the age group the more infected is between 25-30 years followed by the age group 20-25 and then the ages between 30-35. This result is inconsistent with the epidemiological study of hepatitis B at CHU Constantine on the period 2008-2015 by Sandra B et al (Sandra & Nardjess, 2016) which found that the age group the more infected is between 30-44 years.

It is interesting to note from our results, that the rate of HBV infection in children is low compared to that of adults which is high, this low proportion can be explained by the rarity of maternofetal transmission and very low exposure to other modes of transmission at this age (Desenclos et al., 1995)

Our statistical study show that the most common type of hepatitis was the hepatitis B type with a distribution of 95% when compared to hepatitis C with 5%. Our results do not differ from the distribution of cases in the world, as the number of chronic infection with hepatitis B virus is estimated at about 400 million worldwide (about 5% of the world population), while hepatitis C virus infection does not exceed 170 million individuals worldwide (Karnsakul et al., 2017). Through previous research, type C virus is more deadly to type B liver, as it has been proven that genotype C is the most prominent genotype associated with more serious liver diseases (cirrhosis). Production of a large amount of hepatitis B surface antigen molecules that lack DNA that have the potential to integrate into the host genome (Saeed et al., 2014).

Through our results, it appeared that the eastern region known to have a large population density (Derouiche et al., 2020) is the highest in the proportion of patients with viral hepatitis, then the central region, which includes El-Oued city, followed by the southern region that includes Bayada and Robbah, and finally the north and western region .

III.2.Biological marker study

Our results illustrated a significant decrease of erythrocyte line parameters in hepatitis patients when compared with healthy individuals which doesn't correspond with the results of study of (Ekiz et al., 2011), they found that Hemoglobin and hematocrit levels were similar in both groups**.** This decreased values can be explained by a secondary complication, the aplastic anemia ; which characterized by failure of bone marrow induced after an attack of acute B hepatitis. (Bozic et al., 2020)

Moreover, our study showed that the WBC, MONO and NEUT are significantly increased in the hepatitis patients as compared to control. The results found were opposite to those observed in study of (Abdullah, 2018) who demonstrated that the level of WBC decrease without reaching statistical significance, while a statistically significant decrease in neutrophil counts were seen in HBV and HCV positive individuals compared with controls.

A high WBC count is a marker of inflammatory activity in the body (Caplan, 2009), ever higher WBC counts might be an indicator of sepsis occurring in patients with hepatitis B virus related acute-on-chronic liver failure, (Xue et al., 2019)

In particular, Monocytes constitute the first line of defense for external intrusion or infection such as HBV infection. Viral replication takes place inside hepatocytes as soon as infection begins. The secretion of infectious virions or virus proteins can persist for decades at high rates. Interacting with virions or virus proteins, monocytes/macrophages play an important function in the disease process (Lauer & Walker, 2001).

Interacting with virions or virus proteins, monocytes as the first immune barrier, play an important function in the HBV infection process ; (1) act as a pool of precursor cell, which replenish to resident macrophages and dendritic cells as soon as needed, and (2) in response to signals of cytokines or chemokines, monocytes can be recruited and migrated to the sites of infected tissues quickly and divided/differentiated into local inflammatory macrophages and dendritic cells to trigger an immune response and this explain the higher values of monocytes in hepatitis B patients. **(**Haijun & Zhengkun, 2017)

Besides, neutrophils are the first and predominant immune cell population recruited to an affected site after HBV infection, in a process triggered by microbial signals and inflammatory mediators, and they exhibit both protective and pathologic functions (Lekstrom-Himes et al., 2000), also , conventional wisdom suggests that neutrophils enhance antiviral defenses the reason why they are markedly increased in the circulation and tissues during several fungal infections (Tate et al., 2008). Interaction with other immune cell populations, virus internalization and killing, the release of cytokines, chemokines, and antimicrobial components are all mechanisms by which neutrophils can contribute to HBV clearance. (Galani & Andreakos, 2015)

In our experimental study , the result show a significant increase in PLT and MPV with low significant decrease of PDW in hepatitis patients as compared to control, this results are in agreement with the study of (Turhan et al., 2010) who showed that MPV is higher in inactive HBV infection patients than levels in healthy controls (HCs). However, our results are opposite to the findings of (Asghar et al., 2021) who demonstrated that platelet count (PLT) is higher in viral hepatitis patients than in (HCs). According to previous study, increased levels of PLT may be due to sequestration of platelets in the spleen without obvious splenomegaly and portal hypertension (Ekiz et al., 2011) ; because of splenic sequestration, the life cycle of platelets is shorter in patients who have chronic liver diseases such as hepatitis B, however, when the life cycle of platelets is shorter, platelet production increases in the bone marrow, increasing the number of young platelets in circulation **(**Mitchell et al., 2016).

On the other hand, MPV, which describes platelet size, is not only a marker of platelet function and activity but also a novel index of inflammation and its intensity (Gasparyan et al., 2011). several studies have shown that interleukin-6 (IL-6) contribute to hepatic necroinflammation in CHB patients (Wong et al., 2010). Some authors reported increased IL-6 levels are responsible for inducing platelet production , also IL-6 can induce size of platelets by interfering with megakaryopoiesis with subsequent release of big size platelets from the bone marrow (Kaser et al., 2001). Thereby, increased MPV levels may be owing to increased young platelets.

In addition, several studies found an association between increased PLT, MPV and advanced fibrosis in patients with CHB. (Ekiz et al., 2011; Karagoz et al., 2014). The pathogenesis of liver fibrosis is defined as massive production and deposition of several extracellular matrix (ECM) proteins. The accumulation of ECM proteins, as fibrotic scars, slowly distorts liver

structure and increases intrahepatic resistance to blood flow, leading to portal hypertension. As well, thrombocytopenia is a frequent complication of advanced liver fibrosis and is commonly considered to be a secondary phenomenon via associated portal hypertension or reduced production of thromboprotein in the liver. (Friedman et al., 2008 ; Afdhal et al., 2008).

Furthermore, Gasparyan et al. suggested the MPV could be a useful biomarker for inflammation and thrombosis , (Gasparyan et al., 2011). They also consider that increased MPV could be a consequence of thrombosis in patients, along with other risk factors. It is demonstrated in patients with hepatoportal sclerosis that chronic portal microthrombosis might be an underlying mechanism for the development of fibrotic processes in the liver (Hessel et al., 1997 ; Koksal et al., 2007). Taken together with these facts, increased MPV may be the reflection of chronic microthrombosis in the portal bed in patients with advanced fibrosis.

Generally, Increased MPV levels have been reported in patients with metabolic syndromes, which include myocardial infarction, acute ischemic stroke, diabetes, and nonalcoholic fatty liver disease (Ozhan et al., 2010 ; Endler et al., 2002). MPV has also shown to be a sign of inflammation in ulcerative colitis, Crohn's disease, and rheumatoid arthritis . (Ekiz et al., 2011 ; Gasparyan et al., 2011). Korkmaz et al. found that higher MPV may be the consequence of the atherosclerotic process in patients with coronary calcification (Korkmaz et al., 2012)

Conjointly, one can also understand that higher MPV values observed in hepatitis B patients might be another consequence of the association of HBV with the diseases mentioned above.

In our study, we found that the level of total and direct bilirubin is significantly increased in hepatitis patients compared to control group. This results are in agreement with a study of (Atiroglu et al., 2013) who showed a significant increase in the concentration of Serum bilirubin in patients with HBV positive when compared with patient with negative HBV and also with control. Damage of liver cells causes the release of large amounts of bilirubin which increase levels of serum bilirubin. The ratio of direct and indirect bilirubin depends on the degree of hepatocytes damage. (Suljevic et al., 2016).

The present study revealed a higher values of ALP in hepatitis patients than In controls which is in agreement with the study of (Asghar et al., 2021) who found a higher values of ALP in HCV positive and lower values in HCV negative individuals that were within the

normal range. It has been reported in literature that serum ALP level increased with increasing age, body mass index, C-reactive protein, monocyte count, serum uric acid, lead, cadmium, hyper cholesterolemia, diabetes, smoking, non-alcohol drinking, sex, age, liver diseases, lesion of liver and cardiovascular disease. (Hsu et al., 1996). Elevation in serum AP occurs when the hepatocyte canalicular membrane is disrupted, causing translocation from the canalicular membrane to the basolateral (ie, sinusoidal) surface of the hepatocyte and leakage into serum. (Woreta et al., 2014) Most evidence suggests that this elevation primarily occurs because of enhanced translation of mRNA rather than increased synthesis of mRNA in the liver, with subsequent release of the phosphatase into the circulation. This process appears to be mediated by the action of bile acids, which induce the synthesis of the enzyme and may cause it to leak into the circulation, perhaps by the disruption of hepatic organelles and the solubilization of phosphatase bound to such membranes. (Herlong et al., 2011)

The obtained results show a significant increase in AST and ALT levels in hepatitis patient group compared to control and this result is in agreement with finding of (Xianchun et al., 2016). A previous study found that the biochemical analysis (AST, ALT and Total bilirubin) increase with HCV RNA titers and decrease with low HCV RNA titres. (Farag , 2016)

Generally, ALT remained within the hepatocytes, but on damaging of hepatocyte, the enzyme escape out from hepatocytes and raised levels was found in the blood.

It is proved that an increased level of ALT is generally a result of liver disease associated with some degree of hepatic necrosis such as cirrhosis, carcinoma, viral or toxic hepatitis(Hsu et al., 1996), While some studies proved that necrosis of hepatocytes is not necessary the main reason for the release of serum amino- transferases and that the correlation between the levels of liver aminotransferases and degree of hepatocyte damage is weak. (Sanchez et al., 2009)

Persistently normal levels of ALT have been associated with a lower progression and occurrence of cirrhosis in patients with hepatitis. (Woreta et al., 2014) The raised values of AST are found in liver cirrhosis, haemolysis, myocardial infarction, acute viral hepatitis, toxic hepatitis. As Very high values are also obtained in toxic hepatitis due to carbon tetrachloride poisoning and obstructive jaundice. ALT level is also found to be increased with age (Tsang et al., 2008).

As both ALT and AST are associated with liver diseases, liver damage intraoprative hypotension, intraoprative blood loss, liver reseption significantly correlated with liver enzyme elevations (Hsu et al., 1996).

Concerning Uric Acid, results also show that the level of Uric Acid is significantly decreased in hepatitis patients compared to control. The results found were opposite to those observed in study of (Pellicano et al,. 2008) and (Angelos et al,. 2012) who demonstrated that Uric Acid increased in the hepatitis patients.

UA is a risk factor for some chronic diseases, in which oxidative stress plays an important pathophysiological role (Feig et al., 2008). In the same time, UA is a potent endogenous antioxidant and can scavenge various free radicals (Ames et al., 1981; Squadrito et al., 2000). Some prospective cohort studies suggest that UA may be a protective factor against the diseases in which oxidative stress has been implicated (Chen et al., 2009; de Lau et al., 2005) such as CHB disease.

In contrast, it has been shown that UA is involved in chronic inflammation; increased levels of UA may act as a pro-oxidant that activates a complex vicious cycle involving mechanisms related to inflammation and oxidative stress and negatively influences the health (Wu et al., 2015). A previous studies suggests that UA stimulates inflammatory responses by increasing the production of IL-1β, IL-6, and TNFα (Johnson et al., 2003) and by upregulation of cyclooxygenase-2 activity and vascular C-reactive protein (CRP) (Johnson et al., 2003; Watanabe et al., 2002). Higher levels of UA have been repeatedly observed in patients with inflammation-related diseases, such as metabolic syndrome, diabetes and coronary heart disease (CHD) (Choi et al., 2005 ; Culleton et al., 1999; Dehghan et al., 2008). In several studies (Frohlich et al., 2000; Ruggiero et al., 2006), it was observed that UA levels were positively correlated to levels of inflammatory markers as well as a history of chronic inflammation-related diseases (Dorjgochoo et al., 2011 ; Fang & Alderman., 2000; Hershfield et al., 2010)

III.3. Study of oxidative stress markers

In our experimental study, the result show that a significant decreased of reduced glutathione (GSH) in HBV patients as compared with controls group. This result are harmony with the finding of (Vendemiale et al., 2001; Swietek & Juszczyk, 1997).

In the liver, oxidative stress can reverse an imbalance between protein synthesis and the ability of the endoplasmic reticulum of hepatocytes to properly refold and assemble proteins, with increased superoxide production, reduced buffering capacity and / or activity reduced of important antioxidant enzymes, such as glutathione (GSH). (Kakarla et al., 2009).

Generally, Hepatocytes contain about 10% of total body pool of GSH. It is a nonprotein thiol synthesized primarily in the liver, is the main intracellular defense against ROS, free radicals, and electrophilic xenobiotics (Samir et al., 2020 ; Mari et al., 2009). A normal homeostasis of this tripeptide is necessary for the activity of the cytochrome P450 enzyme system and of mitochondria, for the "traffic" from cytoplasm and nucleus and finally for the maintenance of a normal cellular redox status (Mari et al., 2009). GSH also affects the transcription of proinflammatory/anti-inflammatory cytokine genes, liver regeneration through cytokine-mediated nuclear factor binding (NF-B) induction, NO bioavailability, and energy metabolism (Stehbens, 2004)

Moreover, the liver plays a notable role in the redox state, as 90% of circulating glutathione (GSH) levels are produced in this organ (Jones, 2008). With low levels of GSH, mitochondrial function can be impaired and thus several stress-related signaling pathways are triggered, eventually leading to mitochondrial damage, inflammation and steatosis in the liver (Chen et al., 2011). Mitochondria contribute to the formation of ROS, due to increased oxygen consumption during intense exercise. By inducing GSH depletion, ROS induce oxidative stress and reduce the antioxidant capability of other antioxidants (Morris et al., 2013).

As well, the viral activity is enhanced by redox imbalance and peroxidation with virus expression in chronically infected cells. The increase in peroxidation appears to contribute to disease progression with reduction of antioxidant activity that favors further viral replication and potentiates carcinogenesis (Fuchs et al., 1995).

Glutathione's antioxidant system is imbalanced in damage to hepatocytes, so it decreases with disease severity (Levent et al., 2006). Hepatocyte loss varies from random apoptosis to

sporadic or massive cell necrosis, and the more severe oxidative stress, the more active is viral replication and dispersion from lysed or apoptotic cells. Although OS favors viral replication, it is inhibited by antioxidants so in hepatitis progression there are periodic exacerbations. The fluctuating redox balance reflects the nutritional status, concurrent illnesses, xenobiotics, and medicinals (Stehbens, 2004).

Furthermore, in active chronic hepatitis, the remaining viable hepatic tissue depending on the OS severity may have restricted ability to synthesize GSH. It was proved that the decrease in low glutathione levels is more pronounced in acute cases than in chronic hepatitis C infection (Swietek & Juszczyk, 1997; Dikici et al., 2005). In acute cases, there is a relationship between hepatocyte damage and the concentration of GSH, while, in patients with chronic viral hepatitis, the GSH concentration is usually decreased but is not associated with liver damage (Swietek & Juszczyk, 1997 ; Stehbens, 2004)

In addition, Availability of cysteine, the unstable precursor of GSH synthesis in most cells, is a critical determinant of cellular GSH levels, virtually all intracellular cysteine being present in its oxidized form (viz. cystine). The clinically safe thiol antioxidants a-lipoic acid and NAC that enhance cellular GSH levels are beneficial (Sen, 1997), however, in acute and chronic active viral hepatitis, the markedly reduced plasma GSH levels increase on recovery (Stehbens, 2004)

Tanyalcin suggest that due to the disturbed hepatic functions during HBV infection, GSH synthesis is decreased (Tanyalcin, 2000), while, Loguercio et al. propose that an impairment of the trans-sulphuration pathway is the major cause of cystein depletion (Loguercio et al., 1992), but according to Tribble et al., the circulating cystein levels may be influenced by the plasma GSH levels through reduction of cystein (Tribble et al., 1989).

However, HBV-induced ROS induce the releasing of pro-inflammatory cytokines In response to hepatocellular stress, such as tumor necrosis factor (TNF)-α (Esrefoglu, 2012), which, in turn, activates c-Jun N-terminal kinase/stress-activated protein (JNK), JNK down-regulates both the expression and the activity of GPx in HBV-transgenic mice (Wang et al., 2012).

A previous studies have been reported that Hepatitis B virus strongly induces the Nrf2/ARE pathway of antioxidant defense; this activation in the infected cells is achieved by HBx and LHBs proteins of the virus . In the case of HBx, the underlying mechanisms is ROS-

independent and rather implies sequestering of the Nrf2 partner protein Keap1 via formation of a triple HBx-p62-Keap1 complex (Ivanov et al., 2017). Moreover, HBV-infected cells showed increased expression of GS, GR and GCL subunits when compared to non-infected cells. (Vairetti et al., 2021)

However, we can explain the decrease of GSH in hepatitis B patients compared to controls by the engagement of GSH in facing HBV-induced ROS (Anfal & Samir, 2017)..

Malondialdehyde (MDA) is currently considered to the most widely used representative of oxidative lipid damage (Liu et al., 2018). Liver lipid peroxidation levels was measured as malondialdehyde (MDA).(Derouiche et al., 2017). In our experimental study, our data show that MDA level is significantly increased in hepatitis patients compared to controls .This result are in agreement with the studies of (Maria et al., 1996 ; Nadia et al., 2014).

Free radicals generate the lipid peroxidation process in an organism; Malondialdehyde (MDA) is one of the final products of polyunsaturated fatty acids peroxidation in the cells. An increase in free radicals causes overproduction of MDA and its level is commonly known as a marker of oxidative stress and the antioxidant status in hepatitis patients. (Vendemiale et al., 2001).

Particularly, the levels of MDA were elevated in studied HBV patients, this indicates that HBV stimulates the generation of ROS. It had been reported that ROS act as second messenger molecules and key elements to activate the nuclear factor kapa beta (NFKβ) in the early events of inflammation. NFKβ activates the inducible nitric oxide synthase (iNOS) which produces high amount of NO (Ueno et al., 2005). Yoshie & Oshima reported that NO is considered likely to be an important endogenous factor of carcinogenesis, both by itself and also in association with other agents (Yoshie & Oshima, 1998). Hence, it leads to phagocytosis, amplification of inflammation and tissue injury. In addition, it reacts with $O2^{-\cdot}$ producing peroxynitrite (ONOO·), a powerful oxidant, which damage the biological molecules (Yen & Lai, 2002). The generation of O2, NO and other ROS and reactive nitrogen species (RNS) accelerate peroxidation of native membrane lipids leading to loss of membrane integrity, membrane damage and subsequent release of the cytosolic contents (Mittal et al., 2006). In addition, peroxidation of mitochondrial membrane leads to increase the membrane permeability and alteration of Ca2+ homeostasis that contribute to cell death due to alteration in the inner membrane potential (Igbavboa et al., 1989).

It has proved, hepatitis-related liver damage is characterized by increased iron storage (Farinati.1995), which elicits a free-radical mediated peroxidation via the Fenton reaction (Mittal et al,.2006). Level of MDA is also Related with the stage of fibrosis (Serejo et al., 2003 ; Emerit et al., 2000).

Furthermore, in the viral hepatitis, virus also infects the peripheral lymphocytes. The infected lymphocytes produce interferon to stimulate healthy cells against viruses (Tilg et al., 1995). The patients with chronic hepatitis C exhibit an increased production of TNF-α, a cytokine that can produce oxidative stress by stimulating the generation of oxygen ROS (Larrea et al., 1998). Hydroxyl radicals may react by either hydroxylation or hydrogen abstraction, setting off free-radical chain reactions that subsequently increases MDA concentration (Blake et al., 1987).

In a previous study, they found a significant positive correlation between serum MDA and total and direct bilirubin.

Malondialdehyde (MDA) is a major lipid peroxidation product (derouiche et al., 2017). Several hypotheses in relation to the in vivo formation of MDA have been proposed. Pryor and Stanley proposed that oxidized lipids are able to pro-duce MDA as a decomposition product and the mechanism is thought to involve formation of prostaglandins, like endoperoxides from PUFA with two or more double bonds. In 1990, Esterbauer and Cheeseman suggested an alternative mechanism for the generation of MDA, based on successive hydroperoxide formation and β cleavage of PUFA which is the main source of MDA generation in vivo (Esterbauer & Cheeseman, 1990). However other minor sources of MDA formation also exist such as byproducts of free radical generation by ionizing radiation and biosynthesis of prostaglandins (Lykkesfeldt, 2007). During oxidative stress and in many pathological events, enhanced levels of thiobarbituric acid reactive substances (TBARS) have been reported. the studies conclude that all that increases the effect of lipid peroxidation on red cells during oxidative stress leads to a decrease in red blood cells in the body. (Lykkesfeldt, 2007 ; Halliwell et al,.2007).

Met Hb is un-able to bind or carry oxygen, under normal conditions, the level of met Hb in RBCs is maintained at less than 1% of total hemoglobin. However, in high stress conditions, it increases many fold (Arbos et al,.2008). The oxidation of hemoglobin also causes the formation of disulfide cross-links between adjacent globin chains, ultimately distorting the primary structure of hemoglobin which eventually leads to visible precipitates known as Heinz bodies (Winterbourn & Carrell, 1974). At limited oxidative insult, these aggregates of

membrane bound denatured protein can be excised by reticuloendothelial macrophages but greater degrees of oxidation ultimately result in hemolysis of RBCs, if unchecked (Eda et al., 1997). Lipid peroxidation affects hemoglobin due to the occurrence of oxidation in erythrocyte protein. (Sivilotti, 2004)

One of major defenses against RS production is a family of oxido-reductases known as Catalase (CAT). In our experimental study, the result show that a significant increase in CAT activity compared to control groups. The results found were in agreement with the studies realized by (Mirelle et al,. 2012 ; Duygu et al., 1990 ; Ciragil et al., 2011).

Catalase is an antioxidant enzyme which do not only play fundamental but indispensable role in the antioxidant protective capacity of biological systems against free radical attack. The superoxide radical ($O2^{\cdot}$) generated in tissues through metabolism or reactions in cells is catalytically converted to hydrogen peroxide (H2O2) and molecular oxygen (O2) by superoxide dismutase (SOD) (Ighodaro & Akinloy, 2018). H2O2 when accumulated is toxic to body tissues or cells. Also, in the presence of Fe2+ it is converted to deleterious hydroxyl radical ($OH^{\cdot}$) through Fenton reaction. In order to prevent this phenomenon, catalase which is abundant in the peroxisomes breaks down H2O2 into water and molecular oxygen. (Szabó et al,.2007).

The importance of the enzyme can be gauged from the fact of its direct and indirect involvement in many diseases and infections. It has also been reported that catalase is an important enzyme implicated in mutagenesis and inflammation conditions as well as during the suppression of apoptosis which are all known to be associated with oxidative stress conditions (Nandi et al., 2019).

It was reported that catalase effectively reduces HBx protein levels by reducing its stability and accelerating its degradation (Nandi et al., 2019).

Hepatitis B Viruses after entry to the cell by endocytosis commence their intracellular parasitic existence by encoding viral genetic material and using host cell synthetic processes for replication. This disturbs the normal physiological biochemistry of the endoplasmic reticulum and mitochondria with augmented ROS generation and antioxidant depletion resulting in OS of variable severity (Stehbens, 2004).

Thus, reactive oxygen species (ROS) are derived from electron transfer reactions in mitochondria and endoplasmic reticulum (Stehbens, 2003), they include free radicals

(superoxide and hydroxyl radicals) and non-radical species (hydrogen peroxide), which are highly reactive atoms, molecules or ions that contain one or more unpaired electrons that might be formed during a number of physiologic or pathologic reactions and can attack almost every cell component causing further damage to surrounding tissues . ROS are produced during normal aerobic metabolism and their production can be increased dramatically during HBV infection. (Perricone et al., 2009)

The studies show that HBV-mediated ROS production is triggered by three viral proteins, HBx, HBsAg , and HBcAg antigens. (Ivanov et al., 2017)

A previous study found that the oxidative stress induce the activation of c-Abl and Arg which join to the Abl family of mammalian non-receptor tyrosine kinases . (Xiangao et al., 2000)

Cytoplasmic c-Abl is activated in response to ROS production by a mechanism that depends on interactions with protein kinase Cδ. c-Abl is targeted to mitochondria and induces loss of the mitochondrial transmembrane potential . Mitochondrial targeting of c-Abl in response to oxidative stress is also associated with cytochrome c release and induction of apoptosis. (Cao et al., 2003). Arg is also activated in the oxidative stress response and contributes to the induction of apoptosis by interacting with the proapoptotic Siva-1 protein and translocates to mitochondria (Cheng et al., 2003) (Cao et al., 2003).

Generally, little is known about proteins that interact with catalase or the regulation of catalase activity in response to oxidative stress. Despite, It was reported that in response to oxidative stress c-Abl and Arg bind directly to catalase through interactions of their SH3 domains to a PFNP site (amino acids 293–296) that resides on the surface of catalase. (Cao et al., 2003)

In interesting experiment which test the relationship between c-Abl and Arg with catalase, it was found that, with the inhibition of the glutathione redox cycle and compared with control cells, arg $^{-/-}$ cells exhibited somewhat higher intracellular H2O2 levels , increased H2O2 levels were more apparent in c-abl $^{-/-}$ cells . Importantly, even higher levels of H2O2 were found in c-abl $^{-/-}$ arg $^{-/-}$ cells supports more pronounced dysregulation of catalase (Cao et al., 2003) .

However, it was approved that, by association, c-Abl and Arg activate catalase by phosphorylation at both Tyr231 and Tyr386, (Cao et al., 2003) what explain the increase of catalase activity during hepatitis B infection.

H2O2 oxidises SH-groups of membrane receptors, and thus, there is a change in their conformations that can be the reason for the activation of receptors. The activated receptor triggers the intracellular cascade processes at the level of the adenylate cyclase system. This leads to increased cAMP levels in erythrocytes (Revin et al., 2019). In turn, cAMP-dependent protein kinase A, through the mechanism of de- and phosphorylation, it can regulate the activity of many enzymes, including catalase (Hunt et al. 1998).

One of major defenses against RS production is a family of oxido-reductases known as superoxide dismutase (SOD) (Pascotini et al., 2018). Our experimental study demonstrated a significant increase in SOD activity in HBV patient as compared to control groups. This results are in agreement with the studies realized by (Larrea et al., 1998 ; Boya et al., 1999) compared to controls. The Studies of (Loginov et al., 1991 ; Yasuyama et al., 1988 ; Irshad et al., 2002 ; Chrobot et al., 2000 ; Osman et al., 2007) showed a decrease of SOD levels in HBV patients compared to control groups.

It is becoming increasingly clear that certain types of inflammatory tissue damage are mediated by reactive oxygen metabolites (ROM). For example, the administration of specific antioxidants, such as superoxide dismutase (SOD), has been shown to be effective in alleviating the inflammation and tissue damage seen in experimental models of hepatitis (Rosa et al., 2021). The most likely sources of these oxidizing agents are phagocytic leukocytes (eg, neutrophils, monocytes, macrophages, and eosinophils) infiltrating the tissues. Activation of macrophages by interaction with certain pro-inflammatory mediators or specific bacterial products of specific receptors on the plasma membrane of leukocytes leads to the assembly of the flavoprotein NADPH oxidase (Panday et al., 2015). This enzyme catalyzes the production of large amounts of the superoxide fraction. Due to the excessive secretion of the super anion, there is a super increase in the antioxidant activity of the SOD enzyme. (Conner et al., 1996).

The study by Chen et al. who conducted a large study on 93 children with viral hepatitis showed that there was an increase in SOD activity in the acute period in order to protect the body from oxidative damage, while the level of enzymes was decreased in the chronic period of the disease (Chen et al., 2013).

Miyagi et al. found that SOD activity correlates with age, gender, and antioxidant status related to liver pathogenesis (Miyagi et al., 2009). The increase in serum SOD levels may

simply reflect the leakage of the enzyme from the damaged hepatocytes and therefore the severity of the damage to the liver cells (Okrust et al. 1995).

In fact, eukaryotic cells have an extracellular SOD (ECSOD) and two forms of intracellular SOD: one is found in the mitochondrial matrix, the manganese SOD (MnSOD), and another is predominantly present in cytosol, the copper-zinc SOD (CuZn-SOD). (Larrea et al., 1998)

Extracellular SOD is abundant in blood vessels and airways. It accounts for about 70% of the total SOD in certain pulmonary and systemic blood vessels. It is a secretory, tetrameric glycoprotein (mol. wt 135 kDa) and contains Cu and Zn in its active site. Characteristically, ECSOD exhibits heterogeneous affinity for heparin, regulates nitric oxide (NOd) bioavailability, and modulates NO levels. Extra production of SOD may be induced by several mechanisms, of which hyperoxia is the most notable, but inflammatory cytokines such as interferon, tumour necrosis factor (TNF), interleukins (IL) and lipopolysaccharide LPS are important stimulants of SOD production in the intact animal (Andrew, 2017). The expression of ECSOD is depressed by TNF-a, transforming growth factor beta (TGF-b), and IL-1a in cultured fibroblasts (Rahman & Biswas, 2006; Fattman et al., 2003). Copper–zinc superoxide dismutase (CuZnSOD) is the major intracellular SOD, it is a homodimeric protein (mol. wt 32.5 kDa) localized in the cytosol and nucleus that requires both Cu and Zn at its active site for its activity, it acts as a bulk scavenger of superoxide (Fattman et al., 2003) (Rahman & Biswas, 2006)

Mn-SOD is considered to be one of the most important antioxidant components of a cell. It is a homotetrameric enzyme (mol. wt 88 kDa) and requires manganese at its active center. MnSOD constitutes about 10–15% of the total SODs and is located primarily in the mitochondrial matrix (Fattman et al., 2003). Mn-SOD expression appears to be an adaptive response to increased oxidative stress and is enhanced by TNFa, the relationship between ROS and TNFa is bidirectional in that TNFa induces oxidative stress but also ROS activate latent nuclear factor kB29 and increase TNFa expression. In addition to increasing the production of ROS, TNFa also induces the synthesis of Mn-SOD, and this latter effect can protect the cell against the cytotoxic effects of TNFa. (Larrea et al., 1998) It should be considered that Mn-SOD expression is modulated by a diversity of cytokines and proinflammatory mediators in addition to TNFa such as, interleukin-1 and -6 (IL-1 and IL-6) and IFN-g, cigarette smoke, and hyperoxia all have been shown to increase Mn-SOD synthesis. (Larrea et al., 1998) (Rahman & Biswas, 2006) MnSOD has been reported to be

crucial for survival and even 50% expression has been found to provide resistance to hyperoxia. (Rahman & Biswas, 2006)

Production or release of reactive oxygen species by blood vessels or platelets can lead to oxidative stress that supports lipid peroxidation, and induces cellular activation and promotes weak blood vessels (Touyz & Brione, 2011). Superoxide (in the presence of transition metals) enhances lipid oxidation, which leads to the generation of alkoxyl fats and peroxyl radicals and causes lipid radical diffusion reactions (Ayala et al., 2014). As a result of the increase in the production of the superoxide anion, an increase in antioxidant defenses occur, including superoxide dismutase (SOD) (Ighodaro & Akinloy). MPV as a marker of platelet size and activity is one of the most widely used markers. Additionally, MPV has been recognized as an inflammatory marker in cardiovascular, cerebrovascular, rheumatologic, and liver diseases. (Szabo et al., 2007)

Oxygen radical absorbance capacity (ORAC) method is used to measure antioxidant capacity versus oxygen free radicals (Wesołowski et al., 2016). In our experimental study, our data revealed that the total antioxidant activity (ORAC) was increased in serum of hepatitis patient compared to controls which is in agreement with (Pandey et al., 2007).

Reactive oxygen species (ROS) are oxygen-containing molecules that produced during normal metabolism. The organism has enzymatic and non-enzymatic antioxidant systems neutralizing the harmful effects of the endogenous ROS products. In several studies (chrobot.2000), increased oxidative stress has been suggested to be responsible from the hepatocellular damage caused by chronic hepatitis B infection (CHB) (Bolukbas et al., 2005). However, most of them have evaluated oxidative status using individual antioxidants measurement, about the Oxygen Radical Absorbance Capacity (ORAC) assay, it is a method that measures the antioxidant capacity such as CAT and SOD (Moniruzzaman et al., 2011). Anti-oxidant enzyme CAT and SOD levels are increased in hepatocytes of patients with chronic inflammation (Ismail et al., 2010). The significant increase in their levels may point to their role as key enzymes in the protection of the liver from the hazardous products of free radical reactions and may reflect an appropriate activity of antioxidant barrier enzymes as a response to increased oxidative stress (Lykkesfeldt, 2007).

Conclusion & prospects

conclusion

Viral hepatitis has emerged as a major public health problem throughout the world affecting several hundreds of millions of people. Viral hepatitis is a cause of considerable morbidity and mortality in the human population, both from acute infection and chronic sequelae . The development and availability of specific diagnostic reagents will establish the epidemiology of these newly identified viruses, their clinical and public health importance.

The diagnosis of HBV infection and its associated disease is based on a constellation of clinical, biochemical, histological, and serologic findings.

The results of our study showed that Hepatitis B and C diseases is distributed in the different region of El-Oued with more frequent in men 57% than women. Were the most age group to touch are between 20 to 40 years. We observed that the Hepatitis B is the most common type of Hepatitis with frequency 95%. In addition, hepatitis patients are concentrated the most in the eastern and central regions with 37% and 33% respectively.

Through the results of this study, we conclude that this disease leads to a major defect in biochemical parameters such as AST, ALT and in hematological parameters associated with anemia or inflammation, which confirms the importance of these parameters in diagnostic or in Follow-up of Hepatitis disease.

The increase in lipid peroxidation, ORAC levels, SOD and CAT activity, and low level of GSH in serum, confirms the presence of oxidative stress associated with the Hepatitis B disease as a cause or as a development factor for it. Especially what we found a strong relationship between some of these markers with some biochemical and hematological parameters, which is exactly what we concluded through the ROS analysis results that MDA, SOD and CAT are considered to be the most important markers with high specificity and important AUC percentage which contributes to their in early detection of the Hepatitis B diseases.

Prospects:

Given the importance of these results, they open experimental perspectives and other in-depth studies that should allow us to clearly identify to:

- Determine the risk factors of Hepatitis complication in El-Oued region.
- Comparative study of risk factors between El-Oued and other regions.

- Evaluation of other diagnostic markers of Hepatitis.
- Determine the genetic polymorphism of Hepatitis disease in El-Oued.
-Evaluation of the effect of antioxidant supplementation as treatment of Hepatitis diseases.

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Prevalence and Epidemiological Study of Hepatitis B and C Patients Admitted to BEN AMOR DJILANI Hospital in El Oued, Algeria

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ABSTRACT

The Goal of the present study was to evaluate the epidemiological variations of hepatitis B and C in El Oued population. Our epidemiological study was carried out on 1798 hepatitis patients admitted to hospital BEN AMOR DJILANI the period (January 2013 to December 2020) in El Oued region. In Results, 5.45% of patients were aged less than 20 years 72.14% of the patients are aged between 20-40 years, the results also show that 15.85% of patients are between 40-60 years old, and 6.56% of patients over the age of 60 years. On the other hand, we found that the proportion of men among those infected with hepatitis was close to 57.30%, while the proportion of women was more than 42.70%. In this study, there were more people with hepatitis B than type C by 95% and 5%, respectively. Concerning regions of hepatitis patients, the eastern region include the highest number with 37%, followed by - with a small difference - the central region with 33%, then come the southern region with 18%, the northern region contain 11% and at least the western region which include the lowest number of hepatitis patients with 1%, of total cases of hepatitis patients in the state of El Oued. Accordingly, the importance of such epidemiological studies is important to improve the effectiveness of treatment measures to control the disease and thus help reduce the adverse effects of this disease on society.

Keywords: Hepatitis B, Hepatitis C, Liver, Epidemiology, El-Oued

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INTRODUCTION

The notion of viral disease dates back to the end of the nineteenth century, with the identification of diseases transmissible by ultra-filterable and invisible agents in electron microscopy. Viruses, initially defined by their size, are found in all animal species, in plants (including algae and fungi), in bacteria (bacteriophages)[1]. Between the years 1940-1955, Five hepatotropic viruses were discovered as the main causes of viral hepatitis in the world: hepatitis A virus, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus and hepatitis E virus[2]. It appears that more than 185 million people around the world suffer from hepatitis virus infection (C). With fundamental differences between different regions, where, for example, we find the spread of this virus by more than 3.5% in North African and Middle Eastern countries. Also, infection with the virus has several causes. One of

the most important risk factors remains infection with the virus from another person, infection with HIV, or liver infections caused by drinking alcohol[3]. HepatitisC causes a global health problem, as it is the cause of the death of approximately 1.2 million people annually globally, and this is due to the lack of vaccination to this day and the lack of treatments, as we mention some treatments based on direct antiviral agents (DAAs)[4]. The decline in the prevalence of HBV infection may at least in part be related to expanded vaccination, suggested by the largest decline observed in Southeast Asian children[5]. With regard to the methods of virus transmission, there are sexual relations and drug abuse among the main factors for the transmission of this virus between humans[6], and for this reason, appropriate vaccinations must be carried out in case of exposure to these causes, especially in areas where this virus is spread.[7] Lifestyle plays an important role in the etiology of disease, including diet[8]. The virus can cause infection outside the body to another person, and this is by remaining active for7 days. As for the incubation period for the virus inside the body, it ranges from 30 to 180 days, with a rate of approximately 75 days[9]. One of the most important pathological factors in the body is oxidative stress, which results from an imbalance between the production of free radicals and antioxidants[10, 11]. Oxidative stress may affect extra- cellular matrix remodeling, mitochondrial respiration, cell proliferation[12] or hepatitis progressive complication[13]. This article was about an epidemiological study of the distribution of hepatitis B and C patients admitted to BEN AMOR DJILANI hospital from 2013 to 2020 in the state of El Oued.

MATERIELS AND METHODS

The records of all patients diagnosed with hepatitis B and C in El Oued State from 2013 to 2020 were collected from Infectious Diseases service of BEN AMOR DJILANI hospital and information such as the patient's name, age, sex, type of hepatitis and living address was compiled to get the percentage distribution and graphs were drawn for the individual data.

RESULTS AND DISCUSSIONS

The objective of this study is to find out the distribution of hepatitis patients admitted to BEN AMOR DJILANI hospital from 2013 to 2020 in El-Oued. The statistical data can help in the effective prediction of the future trends of hepatitis in El Oued which will help in improving the various treatment options and facilities available for hepatitis patients.A total of 1798 cases of hepatitis patients were analyzed. Based on data collected between 2013-2020 from Infectious Diseases service of BEN AMOR DJILANI hospital, it's were found that man's accounted for 57.29% of the hepatitis population and women's accounted for *42.71%*. In this study, hepatitis occurs to be most commonly affecting the males when compared to the females (Fig 1 and Fig 2).

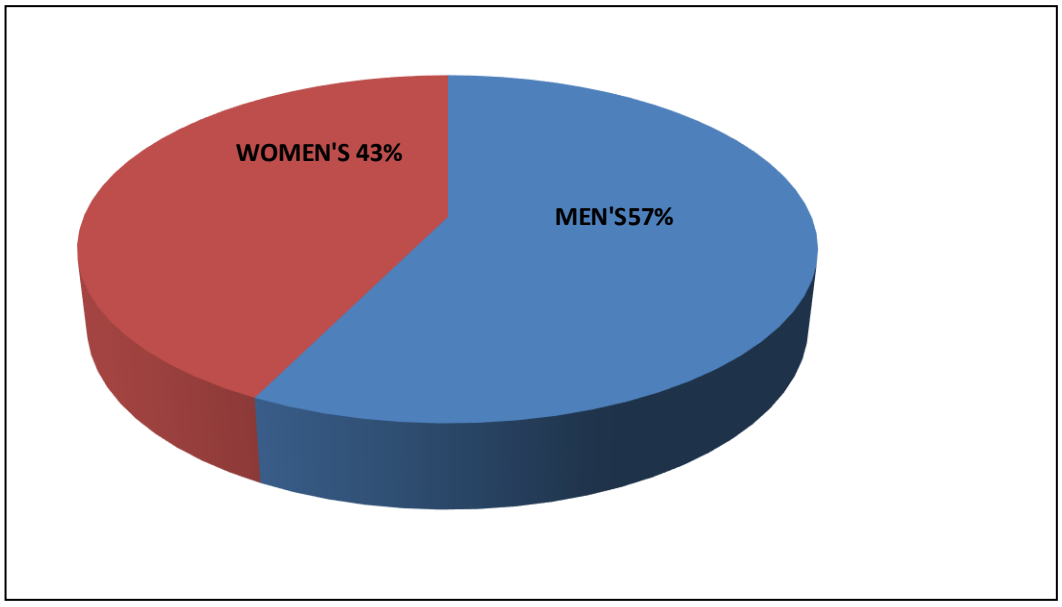

Fig 1: Distribution of the hepatitis patients among men's and women's

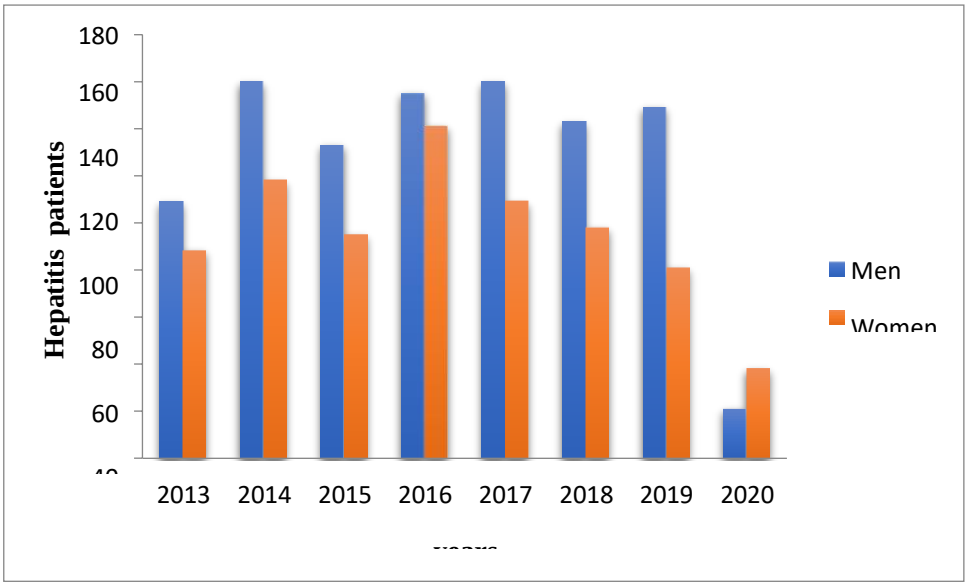

Fig 2: Distribution of the hepatitis patients among women's and men's by years

This result is in concurrence with a study conducted by Tsay et al.[14] which found that the prevalence of serum HBV surface antigen (HBsAg) has been reported higher in men than in women. A similar study conducted by Farza et al.[15] and Breidbart et al.[16] found that female HBV carriers have lower viral loads than male carriers. according to Baruch S et al.[17], Females are more likely than males to produce anti-HBs in response to infection. About distribution of hepatitis patients according to the age, it was found that there were low hepatitis patients (5%) between the age groups 0-20 years of age, 4% of the people between ages 50-55 and 3% of thepeople between ages 55-60.but the highest hepatitispatients were 18% of the people between 20-25 years and 27% of the people between ages 25-30 years in El Oued population (Fig 3 and Fig 4).

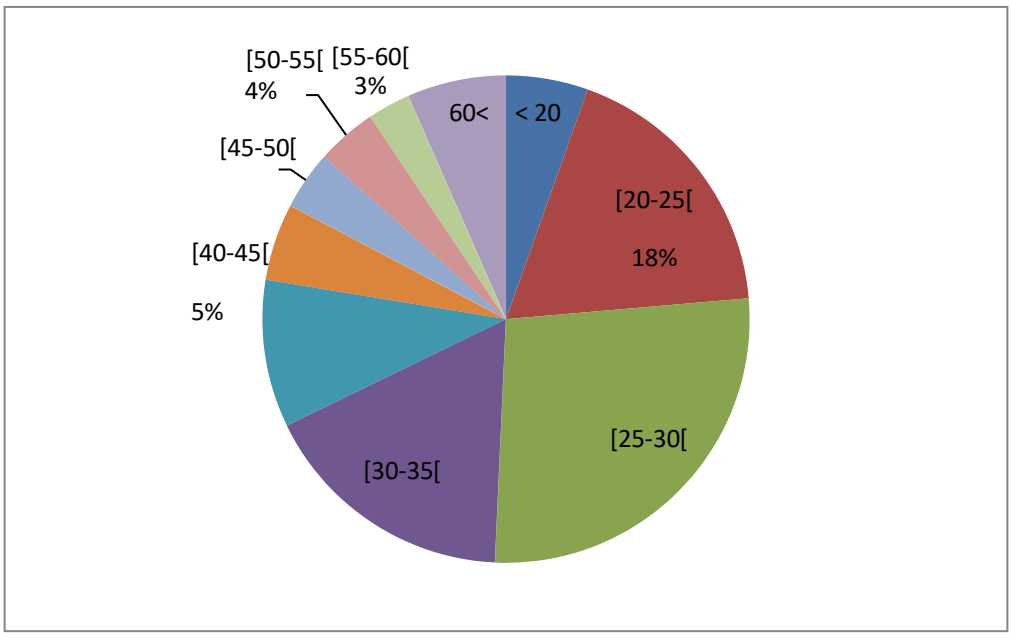

Figure 3: Distribution of hepatitis patients according to the age groups in El Oued Region

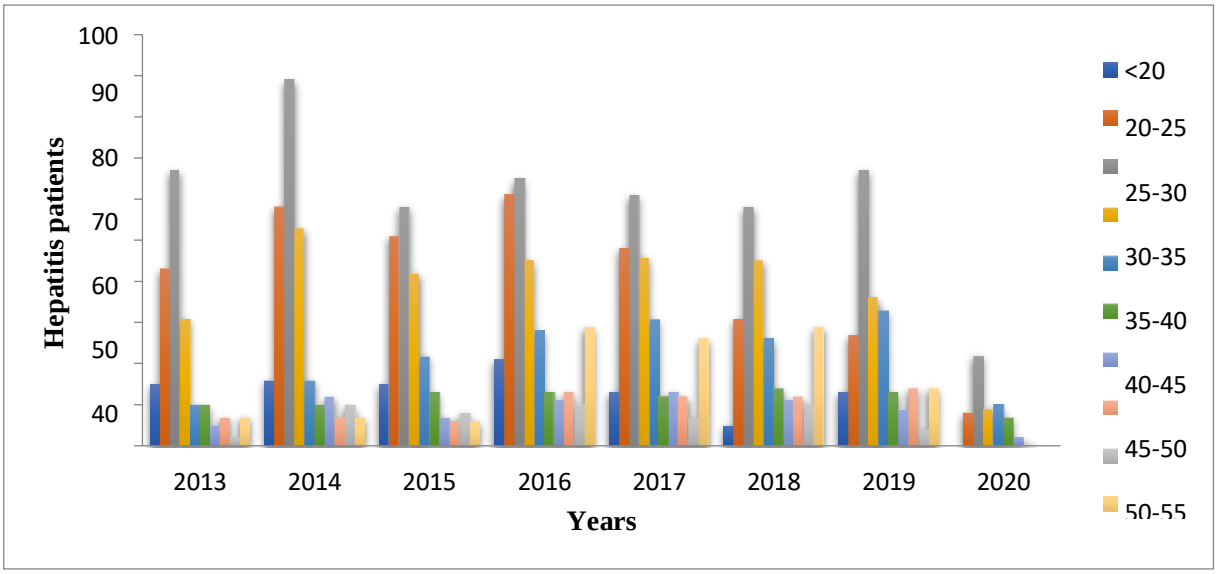

Fig 4: Distribution of the hospital hepatitis patients according to the age group in each year

The age group the more infected is between 25-30 years followed by the age group 20-25 and then the ages between 30-35. This result is inconsistent with the epidemiological study of B hepatitis at CHU Constantine on the period 2008-2015 by Kolou et al.[18] which found that the age group the more infected is between 30-44 years. It is interesting to note from our results, that the rate of HBV infection in children is low compared to that of adults which is high, this low proportion can be explained by the rarity of maternofetal transmission and very low exposure to other modes of transmission at this age[19].

Concerning the distribution of hepatitis patients according to the hepatitis type, the most common type of hepatitis in this study was found to hepatitis B type with a distribution of 95% when compared to hepatitis C with 5% (Fig 5 and Fig 6). Our results do not differ from the distribution of cases in the world, as the number of chronic infection with hepatitis B virus is estimated at about 400 million worldwide (about 5% of the world population), while hepatitis C virus infection does not exceed 170 million individuals worldwide[20]. Through previous research, type C virus is more deadly to type B liver, as it has been proven that genotype C is the most prominent genotype associated with more serious liver diseases (cirrhosis). Production of a large amount of hepatitis B surface antigen molecules that lack DNA that have the potential to integrate into the host genome[21].

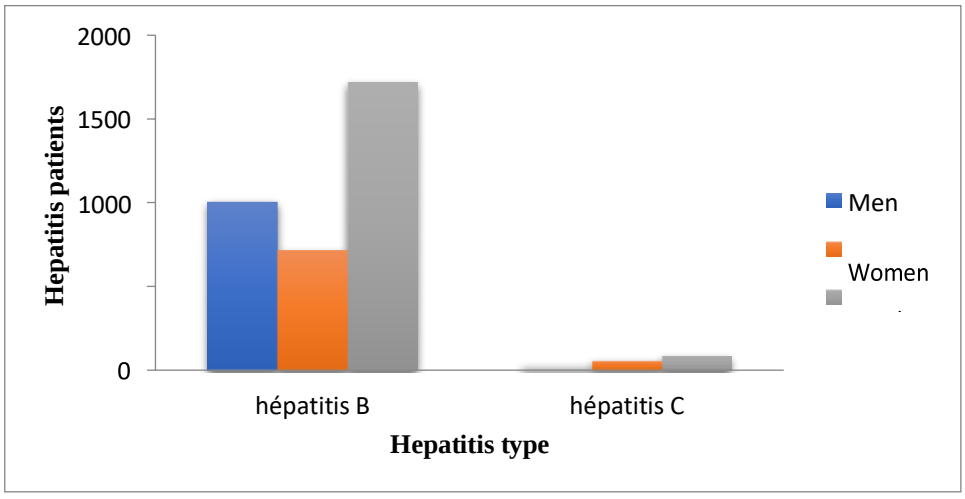

Fig 5: Total distribution and according to the sex of hepatitis patients in each type of hepatitis

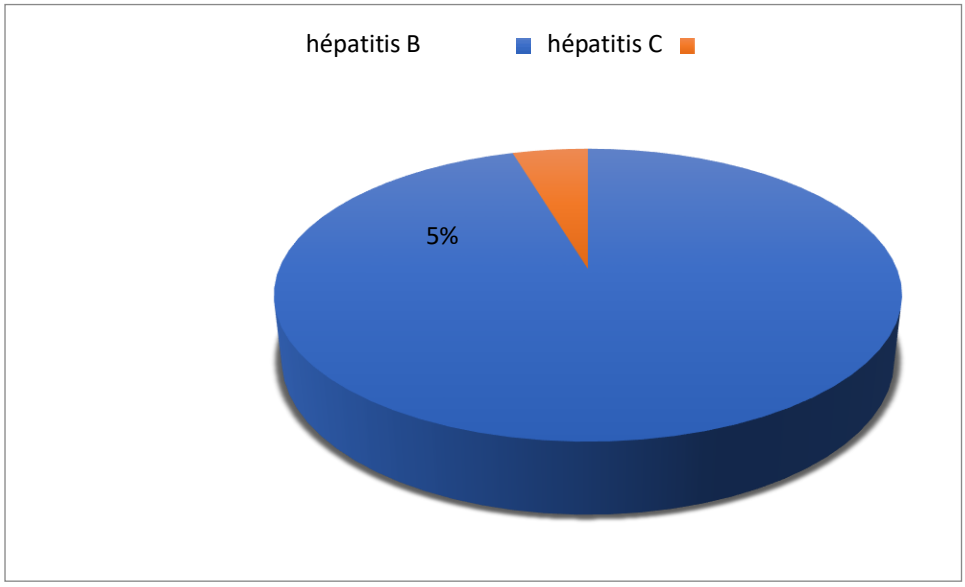

Fig 6: Distribution of hepatitis patients according to the hepatitis type

The results about distribution of hepatitis patients by regions of the state of El Oued, it was found also in this study that 31,15% of the hepatitis patients are from the central region of the state of El Oued. It was found also that 10,62% of the patients are from the North region, 16,91% of the patients are from South region, 35,26% of the patients are from East region and 1,44% of the patients are from West region of El Oued area (Fig 7). The central region is known for its large population density and it consists of the Daira of El Oued[22]. the northern region consists of the Dairas of El M'ghair, Geumar, Reugiba and Djamaa, it is known as a large population density. The southern region has a medium population density and include the Dairas of Robbah and Bayada. The eastern region is known to have a large population density, including the Dairas of Taleb Larbi, Debila, Hassi Khalifa and Magrane. The western region is dominated by the deserts and consists of the Daira of Mih ounsa (Fig 8).

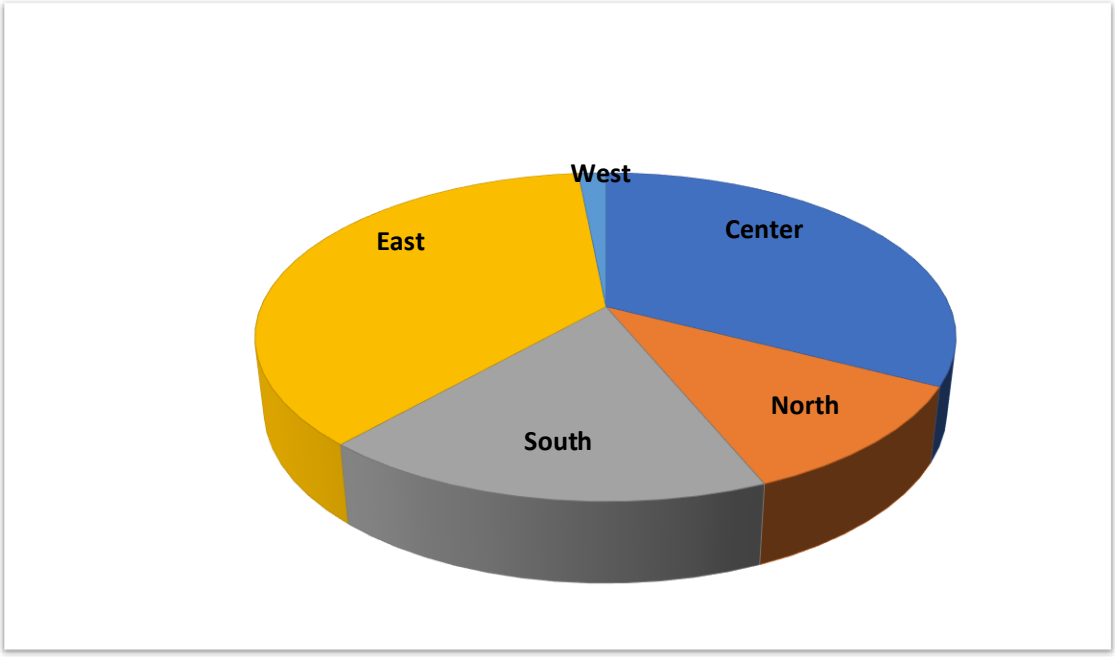

Fig 7: Distribution of hepatitis patients by regions of the state of El Oued

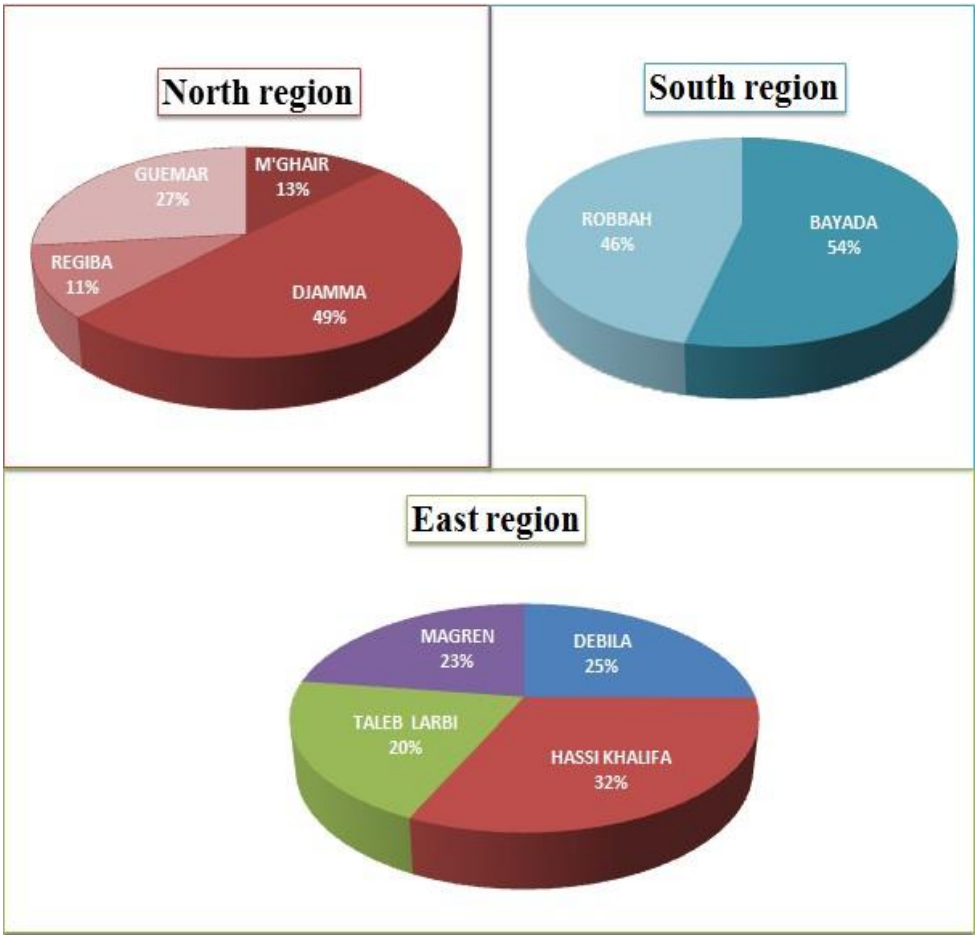

Fig 8: Distribution of hepatitis patients in the different Dairas in each region

Through the results, it appeared that the eastern region is the highest in the proportion of patients with viral hepatitis, then the central region, whichincludes the valley city, followed by the southern region that includes Bayada and Robbah, and finally the north and western region.

CONCLUSION

This study examines the distribution of hepatitis B and C patients admitted to BEN AMOR DJILANI hospitals in El Oued in order to improve the effectiveness of treatment measures to control the disease and thus help reduce the adverse effects of this disease on society**.**

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CONFLICT OF INTEREST

There are no conflicts of interests.

AUTHORS' CONTRIBUTIONS

The conception of the study, drafting the article andinterpretation of data was done by the SM; the otherauthors CM And HN were responsible for the acquisition of data and analysis.

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