DISSERTATION ON

THE STUDY OF LIPID PROFILE CHANGES IN CIRRHOSIS OF LIVER

Submitted To

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In Partial Fulfilment of the Regulations for the Award of

The Degree of

M.D. - GENERAL MEDICINE- BRANCH – I

THANJAVUR MEDICAL COLLEGE,

THANJAVUR - 613 004.

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032.

APRIL – 2015

CERTIFICATE

This is to certify that this dissertation entitled **" THE STUDY OF LIPID PROFILE CHANGES IN CIRRHOSIS OF LIVER "** is the bonafide original work of **Dr. KUMARESAN .S** in partial fulfilment of the requirements for **M.D Branch -I** (General Medicine) Examination of the Tamilnadu Dr. M.G.R. Medical University to be held in APRIL - 2015. The period of study was from **JANAURY – 2014 - AUGUST 2014**.

Prof. Dr. K. NAGARAJAN, M.D.,
Unit Chief M-2
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

Prof.Dr. P.G. SANKARANARANAN,M.D.,
Head of the Department,
Department of Internal Medicine,
Thanjavur Medical College,
Thanjavur - 613 004.

PROF. Dr. P.G. SANKARANARAYANAN, M.D.,
DEAN I/C,
THANJAVUR MEDICAL COLLEGE, THANJAVUR – 613 004

DECLARATION

I, **Dr. KUMARESAN .S** , solemnly declare that the dissertation titled DISSERTATION ON **"THE STUDY OF LIPID PROFILE CHANGES IN CIRRHOSIS OF LIVER"** is a bonafideworkdone by me at Thanjavur Medical College, Thanjavur during Janauary 2014 – september 2014 under the guidance and supervision of **Prof. Dr. K. NAGARAJAN, M.D.,** Unit Chief M-2, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to TamilnaduDr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. degree (Branch -I) in General Medicine**.

Place: THANJAVUR.

Date:

(Dr. KUMARESAN .S)

Postgraduate Student,
M.D. in General Medicine,
Thanjavur Medical College.

ACKNOWLEDGEMENT

I gratefully acknowledge and my sincere thanks to the Dean, **PROF. Dr. MAHADEVAN, MS** Thanjavur Medical College, Thanjavur, for allowing me to do this dissertation and utilize the institutional facilities.

I am extremely grateful to **PROF. Dr. P. G. SANKARANARAYANAN .,**Head of the Department, Department of Internal Medicine, Thanjavur Medical College, for his full-fledged support throughout my study and valuable suggestions and guidance during my study and my post graduate period.

I am greatly indebted to **PROF. Dr. K. NAGARAJAN MD** my Professor and Unit Chief, who is my guide in this study, for his timely suggestions, constant encouragement and scholarly guidance in my study and post graduate period.

I profoundly thank my professors **PROF. Dr. S. MANOHARAN, M.D; PROF. Dr. C. GANESAN, M.D, PROF. Dr. D. NEHRU, DMRD, M.. Dr. GUNASEKARAN, M.D D.M.,** (Registrar), for their advice, guidance and valuable criticism which enabled me to do this work effectively.

I would like to express my gratitude to **PROF. Dr. R. GANESAN MD DM** Department of Gastroentrology for his immense help in the study which enabled

me to complete this work and also permitting me to utilize the facilities available in the department.

My sincere thanks to assistant professors **Dr. J .VIJAYABABU SATHISHKUMAR MD**,**DM., Dr. S. VETRIVEL, M.D.,DCH, DDVL** for their motivation, encouragement and support.

I am also thankful to **Dr. RATHA, MD, DM** for spending their valuable time in giving UGI scopy reports for my study.

I am also thankful to all lap technician and paramedical staff help do my study.

A special mention of thanks to all the patients who participated in this study for their kind cooperation without whom the study would not be possible.

I would like to thank my colleagues and friends who have been a constant source of encouragement.

I express my heartful love, thanks and sense of gratitude to God and beloved parents, my wife **Dr. K. Ilavarasi MBBS., DO** and my dear son with my dearest family members for their kind cooperation and help extended during my research tenure.

I praise almighty who has bestowed me the grace, courage and strength to achieve this target. Last but not least I want to thank all those who have helped me directly or indirectly to make this work a success but missed a mention.

CONTENTS

ABSTRACT

Background:

Cirrhosis is often associated with impaired lipid metabolism. However ,there are only a few studies regarding lipid profile in cirrhosis that have been undertaken in India. The aim of the study is to assess the degree of alteration of serum lipid profile in cirrhotic patients and also to detect its relationship with the complication of cirrhosis and assess the severity.

Materials asnd Methods:

This prospective study was conducted in 50 cirrhosis patients admitted in Thanjavur medical hospital .A questionnaire of personal characteristics including history of alcoholism , detailed present and past history was elicited for each patient. Serum lipid profile (total, low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol and triglyceride) was recorded.

Lipid levels in our study was correlated with the complications of cirrhosis .Statistical analysis was done using T –test.

Results:

Majority of the cases were in the 41-50 years age group. In patients with cirrhosis, the total serum cholesterol level was decreased. There was a significant decrease in serum HDL and LDL cholesterol and triglyceride levels . This low lipid level was

scompared with various complications of cirrhosis and the data was statistically analysed and it shows no correlation between complications and low lipid levels.

Conclusion:

In this study, we found that there was marked reduction of serum lipid profile values in patients with cirrhosis. Therefore, a search for lipid profile abnormality should be performed in every cirrhotic patient. There was no significant correlation between the serum lipid values and the incidence of complications of cirrhosis.

Key words: Cirrhosis, serum lipid profile complication.

1. INTRODUCTION

Cirrhosis of liver is a very common disease which clinicians encounter both at primary and tertiary care. Cirrhosis is a degenerative condition of the liver in which normal hepatic tissue is replaced by anatomically abnormal structures, which eventually impair liver function.

Liver cirrhosis represents the advanced stage of hepatic injury caused by chronic liver diseases such as hepatitis and alcoholic liver disease and various other causes and may gradually progress towards end-stage liver failure even liver cancer.

In the early 1920s, the cirrhotic mortality rates declined steeply in the United States due to the introduction of the national Prohibition act (Ban on the sale, production and transportation of alcohol). However, once the Prohibition was ended, the mortality rates increased again until the mid-70s, when people realized the consequences associated with alcohol abuse and started participating in AA (Alcoholics Anonymous) meetings.

Reduced exposure to hepatitis infections also attributed to the declining cirrhotic mortality rate from the 70's. Similar time trends were observed for European countries, with the exception of the United Kingdom and some Nordic

countries. Especially the high cirrhotic mortality rate across Scotland, where the overall alcohol consumption doubled over the past four decades, remains extremely alarming. With no effective treatment, at least not for advanced and irreversible stages, liver cirrhosis becomes a global health issue, accounting annually for an estimated 800000 deaths worldwide.

Exact incidence rates are difficult to estimate as cirrhosis often remains unnoticed until end-stage liver failure has occurred. However, in Belgium, about 84000 patients were diagnosed with cirrhosis in 2008 and 2009, of whom 4769 patients died in a Belgian hospital. Although several treatments (Antibiotics, healthy diet, abstaining from alcohol etc.) attempt to restrict further disease progression and reduce complications, liver transplantation is the only appropriate option when the liver ceases to function or complications are no longer suppressible.

But even after liver transplantation, long-term survival of the patient is not guaranteed as alcohol relapse or liver rejection may occur. To offset the risk of relapse, patients suffering from alcoholic cirrhosis are commonly only eligible for a liver transplant after establishing a 6 month period of abstinence from alcohol.

Lipids are one of the necessary components which control cellular functions and homeostasis. Liver plays an essential role in lipid metabolism, several stages of lipid synthesis and transportation.

The liver plays a key role in the metabolism of plasma lipids and lipoproteins. As majority of endogenous cholesterol is synthesized in the hepatic microsomes. Synthesis and metabolism of cholesterol is impaired in chronic liver disease resulting in a decrease in plasma levels. Severe metabolic impairment in cirrhosis can produce a worsening of the serum lipoprotein pattern. High‐density lipoprotein (HDL) cholesterol and its major Apo lipoproteins have been shown to be reduced in cirrhosis, as also the serum levels of low‐density lipoprotein (LDL) cholesterol.

Hence this study aims at studying the lipid profile changes in Cirrhosis, thereby reassessing the need for lipid profile in all the patients as a prognostic tool.

AIMS AND OBJECTIVES

- The study of lipid profile [Total cholesterol (TC), triglycerides (TG) high density lipoprotein (HDL), low density lipoprotein (LDL) and very low density lipoprotein (VLDL)] changes in cirrhosis of liver.
- Correlation of lipid changes with various complication of Cirrhosis.
- To assess the severity of Cirrhosis related to lipid profile changes.

2. REVIEW OF LITERATURE

2.1. HEPATIC ANATOMY

The liver- Hepar in Greek, is the largest parenchymal organ, weighting approximately 1.2 - 1.5 kg even at rest, the liver receives up to 25% of the total cardiac output (1), indicating its major role in the metabolism and its necessity for survival. Various metabolic and detoxifying functions are carried out by the liver. As the main site of glycogenolysis and gluconeogenesis, the liver is involved in regulating the blood sugar level. Other metabolic functions include the breakdown of proteins and lipids, and the synthesis of cholesterol and triglycerides.

The most prominent detoxifying function of the liver is the biotransformation of lipophilic substances (Medication, nutrition additives, steroid hormones etc.) in order to make them more water-soluble and thus to increase the possibility of excretion. The liver also produces daily about 500 ml of bile, which either drains directly into the duodenum or is temporarily stored in the gallbladder. The liver relies on liver cells as well as on three mass transport systems to ensure the metabolic work load and the removal of drugs and toxins from the blood. The mass transport systems consist of the vascular system, the biliary system and the lymphatic system.

2.1.1. HEPATIC BLOOD SUPPLY

Unlike other organs, the liver's vascular system is composed of two supplying blood vessels, the hepatic artery and the portal vein. Both vessels ramify at the level of the liver hilum in branches towards the right and left lobe. The hepatic artery provides the liver with oxygenated blood, accounting for nearly one third of the total blood flow to the liver.

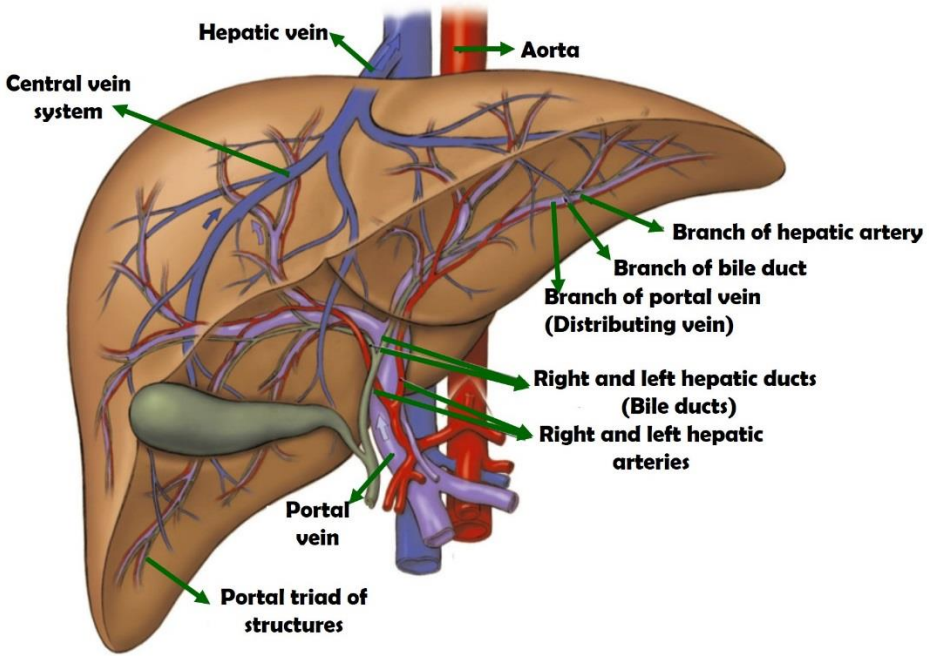


Fig: 1. Blood Supply of Liver

The remaining blood supply is delivered by the portal vein and contains nutrient enriched but partially oxygen depleted blood from the intestines. Venous drainage of the liver is assured via the hepatic veins. The hepatic arterial buffer

response (HABR) is a mechanism to regulate the hepatic blood supply. Alterations in the portal flow are compensated by changes in hepatic arterial flow in order to ensure a constant hepatic blood flow. The mechanism depends on the amount of adenosine locally washed away by the portal blood flow, resulting in either arterial dilation or contraction (2).

The hepatic biliary tree counts two hepatic bile ducts emerging from the liver. Both unite in the live hilum to form the common hepatic duct, which guides the bile produced in the liver into the duodenum (1). The liver also produces a large amount of lymph, which is mainly produced at a microstructural level (The sinusoids). As a consequence, the liver has a deep lymphatic network to ensure the drainage of the lymph directionally towards the heart (3).

2.1.2 FUNCTIONAL ANATOMY

2.1.2.1 HEPATIC LOBULE

The liver lobes are on a microstructural level, composed of repetitive anatomical units called lobules (4). The lobules resemble the shape of hexagonal prisms, which are penetrated by portal tracts at the periphery and central veins in the centrum. The different vessel systems are separated by approximately 0.5 mm (5). Portal triads contain the terminal intrahepatic ramifications of the portal vein,

hepatic artery and bile duct (Respectively portal venule, hepatic arteriole and a bile ductule).

2.1.2.2 HEPATIC ACINUS

When looking from a metabolic perspective to the microcirculation, one of the proposed functional units is the hepatic acinus (6). The acinus is centered on a line connecting two terminal portal tracts and is divided in different metabolic zones.

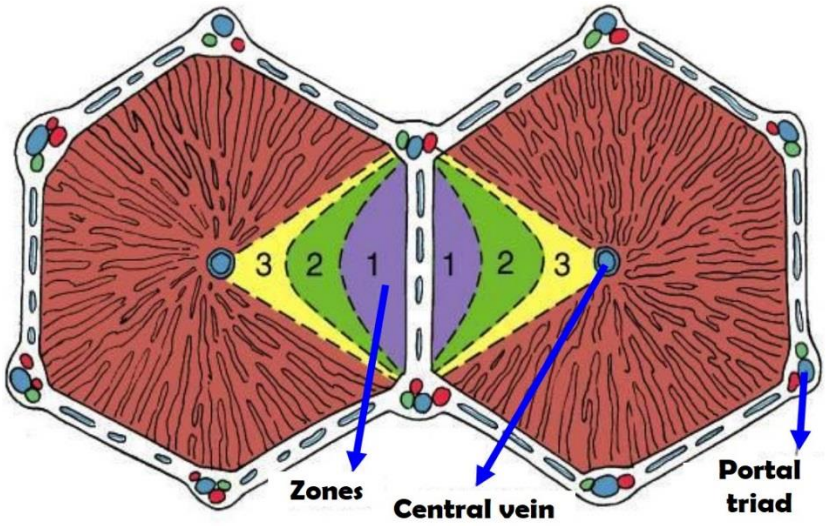


Fig: 2. Hepatic Acinus

The periportal zone I is situated closest to the arriving oxygenated blood flow. Therefore, zone I hepatocytes are specialized in oxidative liver functions (e.g. gluconeogenesis). The centrilobular zone III, on the other hand, receives

blood of inferior quality and thus may suffer most from ischemic injury. Although this region is easily subjected to damage, it still provides a significant contribution to the detoxification of blood.

Hepatocytes residing in zone II have functional and morphological properties intermediate between cells of zones I and III. Hence, hepatocytes contained within zone I survive longer and may form the basis for liver regeneration after partial hepatectomy or hepatocellular damage.

This well-orchestrated regenerative response of the mature functioning cells enables the liver to restore lost tissue up to two third of its total mass, while simultaneously performing vital functions to maintain the body homeostasis (7 & 5).

2.1.2.3 RHOMBOIDAL ACINUS

The rhomboidal acinus is located on the line connecting two terminal portal triads consisting of a portal venule, hepatic arteriole and bile ductule. Zones I, II, and III represent metabolic regions increasingly distant from the blood supply. Zone I receives blood with the best quality with regard to oxygen and nutrients. The circulatory peripheral zone III suffers most from injury (8).

2.1.2.4. SINUSOIDAL CELLS

The sinusoids are lined by endothelial cells, which contain no basal lamina. Plasma constituents gain access to the sub endothelial space of Disse due to fenestrae (approximately 0:1µm in diameter) acting as transport pores in the continuous endothelial lining.

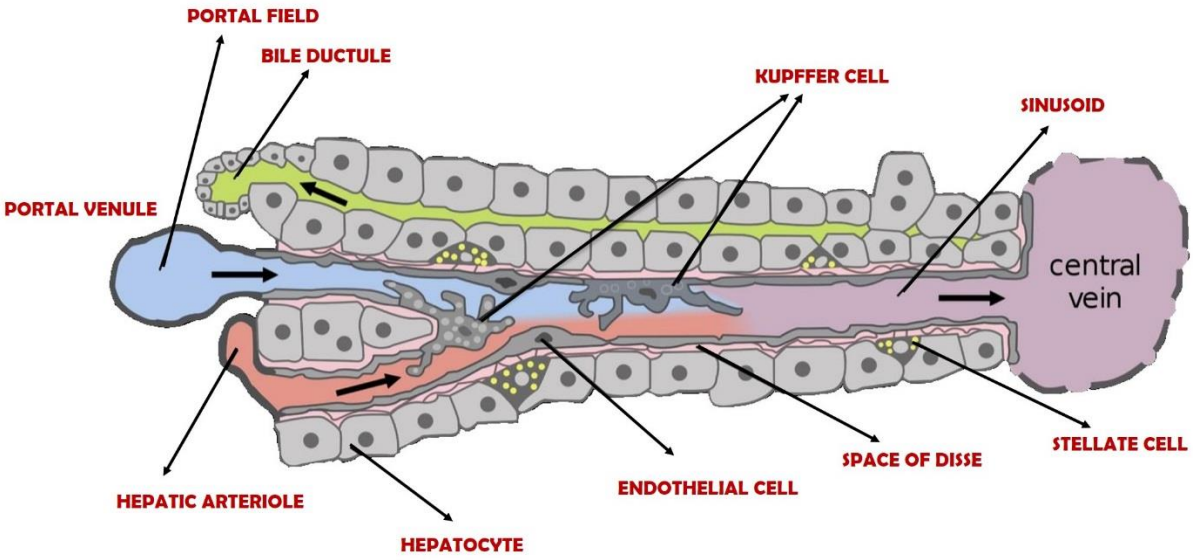


Fig: 3. Rhomboidal Acinus

The space of Disse is composed of permeable connective tissue and is situated between the hepatocytes and the sinusoids. Fenestrae have a dynamic cytoskeleton to preserve and control their size, which can be influenced by various factors like alcohol, nicotine, etc. Hence, a graded barrier is formed, keeping macromolecules and red blood cells within the vascular space due to their size.

White blood cells, however are able to migrate through the endothelial cells into the space of Disse and thence to the periportal region where lymph vessels in the connective tissue ensure their return into the bloodstream. Moreover, pinocytosis, carried out by the endothelial cells, enables the clearance of other vital (macro) molecules from the circulation. Sinusoids thus form a vascular bed that functions as a biofilter. The extracellular matrix may alter the sinusoidal capacity to sieve the passing blood particles as it influences the diameter of the endothelial fenestrae (5).

2.2 CIRRHOSIS

The liver is an organ that can withstand a certain degree of damage, because of its remarkable ability to regenerate lost tissue after injury. However, in case of cirrhosis, repeated insults or chronic liver disease diffusely damages the liver cells in the whole organ, causing inflammatory changes which result in cell necrosis.

As a reaction to the damaging process, fibrogenesis is activated to cooperate in the wound healing process. In addition, hyperplasia of the surviving cells eventually occurs leading to the formation of hepatocellular nodules. As injury to the liver cells advances, progressive scarring of the liver and distortion of its architecture manifests, causing hepatic impairment. Cirrhosis tends to get worse over time and may even become life threatening. Despite several attempts, no all-encompassing definition exists to describe cirrhosis in all its aspects.

The currently most used definition dates back from 1978 (Anthony) and is exclusively defined in morphological terms:

Cirrhosis is a diffuse process characterized by fibrosis and the conversion of normal architecture into structurally abnormal (regenerative) nodules (9).

Two independent characteristics, the connective tissue septa and regenerative nodules, account for the main pathophysiologic chronic condition of cirrhosis, irrespective of its etiologic starting point. Despite the fact that parenchymal necrosis is omitted from the morphological definition, it is generally presumed that a large part of the fibrosis synthesis is the result of necrosis. Necrosis is therefore an essential feature as it entails not only the premature death of cells but also the accompanying environmental reactions to and the disappearance of dead cells.

The term cirrhosis thus implies an alteration of the hepatic circulation and is traditionally assumed to be irreversible. In contrast, a recent study indicates that cirrhosis regression or even reversal can be achieved after the successful treatment of the underlying liver disease coupled with antifibrotic agents.

2.2.1. ETIOLOGY

Cirrhosis is defined as widespread fibrosis and nodule formation. Congenital hepatic fibrosis consists of fibrosis without nodules. Partial nodular transformation consists of nodules without fibrosis. Cirrhosis is a dynamic and complex process which may be evoked by nutritional deficiencies, chemical agents and lack of oxygen, viral and bacterial infections and metabolic disturbances. The most common diseases that give rise to cirrhosis include chronic hepatitis, fatty liver disease and chronic biliary disease (10). Alcoholic liver disease and hepatitis C are the predominant causes of cirrhosis in Western countries, whereas the prevalence of hepatitis B-induced cirrhosis is vastly increasing in developing countries. Since the detection of the hepatitis C virus and non-alcoholic steatohepatitis, cirrhosis of which the etiology cannot be diagnosed (Cryptogenic cirrhosis) only rarely occurs (11). Often, co-factors including age, sex, obesity, alcohol and genetic factors interact with the prevailing cause. Alcohol consumption, for instance, may severely increase the likelihood of disease progression in patients with hepatitis B or C (5). The following are various causes of Cirrhosis.

- Viral hepatitis (A, B, C, D, E and G)
- Alcohol
- NASH

- Metabolic iron overload (HFE haemochromatosis)
- Copper overload (Wilson ’s disease)
- Alpha 1 - antitrypsin deficiency
- Type IV glycogen storage diseases
- Galactosaemia
- Tyrosinaemia
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Hepatic venous outflow block (Budd – Chiari syndrome)
- Heart failure
- Autoimmune hepatitis
- Toxins and drugs, e.g. methotrexate and amiodarone

Many liver diseases have a major initiating factor and a number of co - factors contributing to the development of cirrhosis.

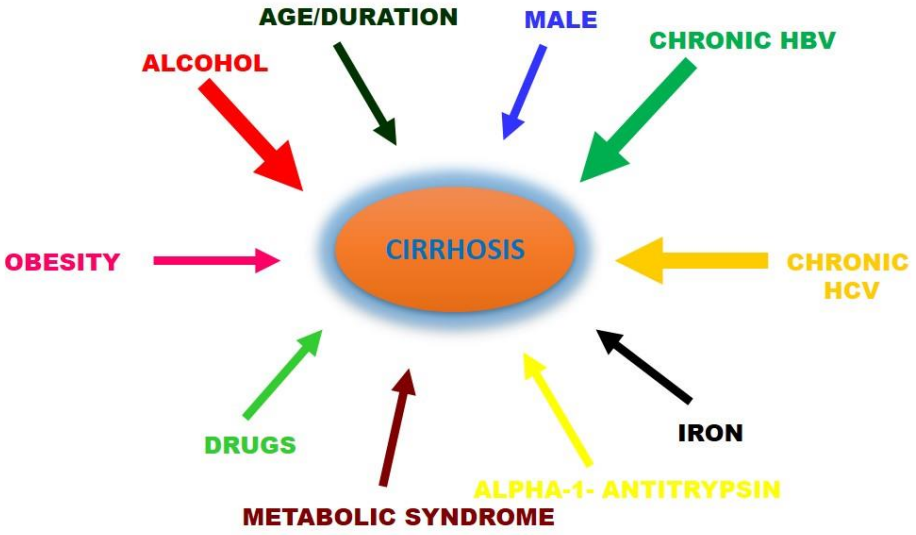


Fig.4. Co - Factors for Development of Cirrhosis

Patients with insulin resistance or diabetes mellitus, or who are immune suppressed, are at higher risk for developing cirrhosis from several etiologies. Thus in many cases there can be a principal factor and interacting co - factors which cause a patient to develop cirrhosis. The relative importance of these co -factors may vary from patient to patient (5).

2.2.1.1. CHRONIC HEPATITIS

Common forms of chronic hepatitis include hepatitis B, hepatitis C and autoimmune hepatitis. Pathological features that arise in chronic viral hepatitis comprise parenchymal cell necrosis and periportal inflammation.

2.2.1.1.1. HEPATITIS C

The hepatic C virus (HCV) most likely evolves a mechanism to interfere with immune signaling pathways and to prohibit antiviral actions. As such, the virus enables the evasion of the host innate and adaptive immune response inside infected hepatocytes. In addition, cytotoxic activity of natural killer cells towards HCV-infected liver cells is down regulated. So once chronicity is established, the virus can persevere despite the presence of cytotoxic T lymphocytes (CTL) and, moreover, it is believed to be insensitive to antiviral cytokines. However, infected and inflamed areas still initiate fibrogenesis through activation of hepatic stellate cells with cytokines and other signaling molecules. Regions around the portal tracts are primarily affected, the fibrosis thereafter gradually extends out into the lobules towards the central veins (5).

2.2.1.1.2. HEPATITIS B

The pathogenesis of hepatic B virus (HBV)-related liver injury is driven by complex interactions between the virus and the host immune response. Patients affected with chronic hepatitis B do contain antibodies against hepatitis B, however, these antibodies are not enough to overpower the infection. The virus manages to infiltrate hepatocytes through endocytosis. Its continued reproduction inside hepatocytes causes the adaptive immune response, in particular virus

specific CTLs, to react in an attempt to purify HBV from affected hepatocytes. The killing of infected but viable liver cells contributes to most of the hepatocellular necrosis (12 & 5).

2.2.1.1.3. AUTOIMMUNE HEPATITIS

Autoimmune hepatitis occurs when the host immune system invades hepatic cells. Genetic predisposition or acute liver infection may be underlying reasons. The abnormal immune response leads to liver inflammation and cell necrosis. Both hepatitis B and autoimmune hepatitis are considered high grade necro inflammatory diseases, as opposed to hepatitis C. Therefore, large regions of parenchymal extinction are commonly produced by the former (5).

2.2.1.2. ALCOHOLIC FATTY LIVER DISEASE

Sustained alcohol abuse favors the development of alcoholic fatty liver disease. Excess alcohol intake leads to an increased oxidative stress via generation of reactive oxygen species (ROS). Some of the consequences of increased ROS include altered mitochondrial activity, DNA damage, the destruction of membranes via lipid peroxidation, and the release of pro inflammatory cytokines.

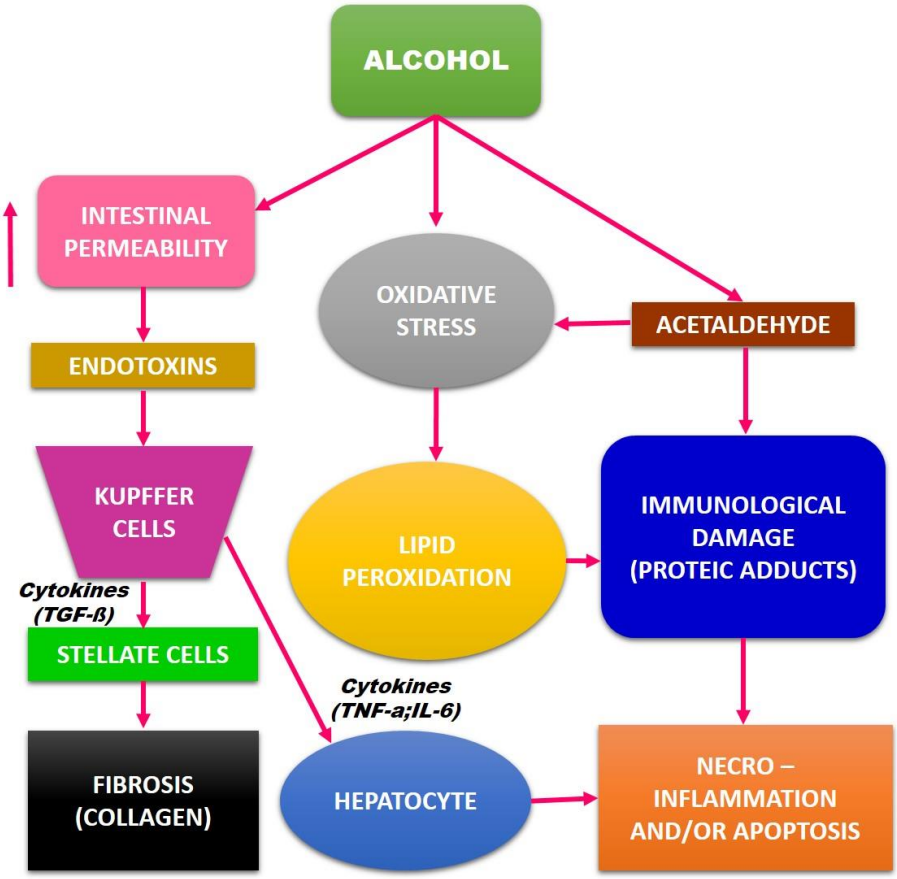


Fig.5. Mechanisms of ALD

The impaired oxidative capacity of the mitochondria leads to accumulation of intracellular lipids, thereby evoking steatosis. The vesicular fatty changes are often accompanied by progressive liver inflammation (13). High-ethanol blood levels also enhance the oxygen uptake and metabolization by liver cells. The blood flow, however, cannot comply with the increased oxygen demand. In addition, ethanol induces diminished release of nitric oxide (NO) in the cirrhotic liver. The decreased NO levels promote intra hepatic vasoconstriction and portal

hypertension. Both oxygen deficiency and reduced perfusion cause a hypoxic state in centrilobular regions of the liver lobule.

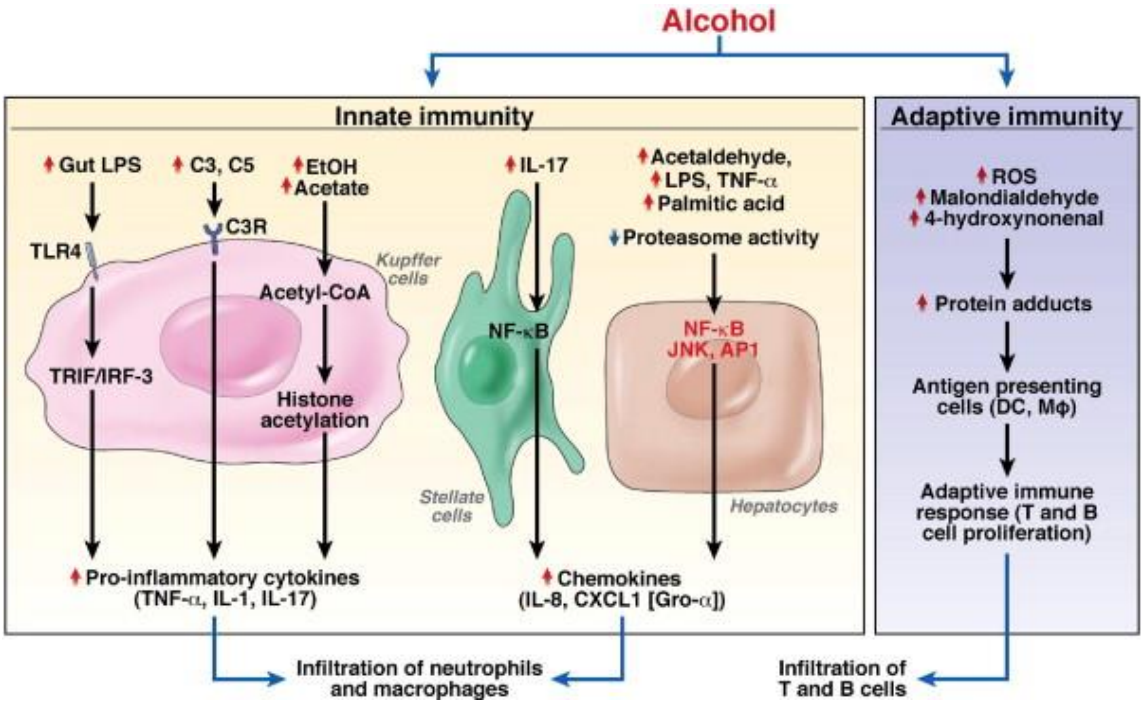


Fig.6. Pathogenesis of ALD

Disorders of energy metabolism, ensued from either hypoxia or decreased mitochondrial activity, can lead to hepatic injury (5 & 13). Furthermore, chronic alcohol consumption increases the absorption of bacterial endotoxins. The endotoxins, in turn, sensitize Kupffer cells, causing the exaggerated transcription of proinflammatory cytokines (TNF-a, IL-6 and TGF-b).

The cytokines promote activation of stellate cells and induce necroinflammation or apoptosis, leading to collagen synthesis and hepatocyte

ballooning (liver cell degeneration due to swelling and enlargement). Sinusoidal fibrosis is often associated with alcoholic fatty liver disease, as it predominates in the centrilobular zone situated around terminal hepatic vein (13).

2.2.1.3. NON-ALCOHOLIC FATTY LIVER DISEASE

Non-alcoholic fatty liver disease is commonly diagnosed in people with diabetes and obesity. The relatively benign disease, which is related to metabolic syndrome, can progress to inflammation of the liver and concomitant fat accumulation (5 & 14).

2.2.1.4. CHRONIC BILIARY DISEASE

Chronic biliary diseases are marked by extra- or intra hepatic cholestasis. Though prolonged biliary obstruction usually causes the inflammatory destruction of bile ducts, metabolic disturbances (Genetic defects and medications) are also considered as underlying causes. The progressive damage to the ducts impairs the drainage of bile acids. Biliary products accumulate in the liver and, when leaking outwards, damage the normal tissue. A network of fibrotic septa connecting enlarged portal triads are often found in biliary cirrhosis. Other cirrhotic features, including regenerative nodules and anastomoses, are rarer and less developed (14 & 10).

2.2.2. PATHOGENESIS

2.2.2.1. FIBROGENESIS

Fibrogenesis is an innate reparative process that contributes to the natural wound healing response in injured tissue. Fibrous connective tissue is produced in an attempt to limit and encapsulate the damaged area. However, sustained signals associated with chronic or repetitive hepatocellular injury result in excessive formation of scar tissue. Persistent accumulation of fibrosis can eventually cause the development of cirrhosis (13 & 15).

The evolution of a normal to fibrotic and subsequent cirrhotic liver is a complex process engaging several hepatic cells and mediators to restrict the damage. The progression of fibrosis can vary among individuals and depends on the cause of hepatic injury. In addition, factors including alcohol consumption, male gender and greater age at the time of infection are all associated with ‘rapid fibrosers’. Genetic determinants may also contribute to variable progression rates (5).

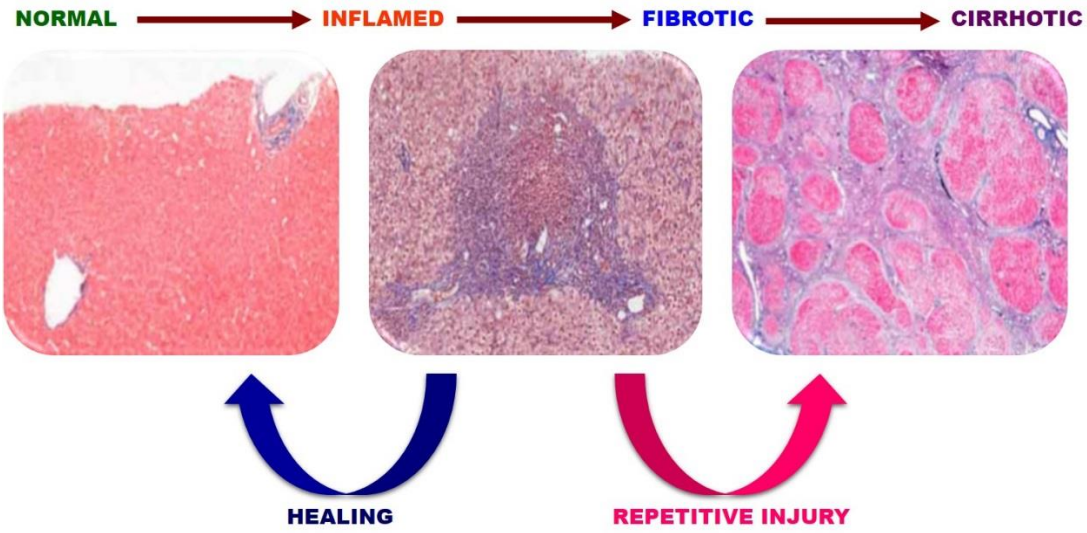


Fig. 7. Fibrogenesis of liver

In the normal liver, strands of type IV (non-fibrillary) collagen are present in the space of Disse among other low-density components to provide cellular support and molecular signals.

The low-density connective tissue matrix and fenestrated basement membrane thus enable the unhampered exchange of substances between the sinusoidal lumen and hepatocytes. After hepatic injury, a vast increase in high-density fibril-forming collagen (type I and III) deposition is observed along portal tracts, in spaces of Disse and in regions of necroinflammatory collapse.

The growing accumulation of type I collagen, key characteristic of fibrogenesis, originates from both reduced degradation and increased synthesis. The hepatic stellate cells (HSC) and portal fibroblasts are the main cell types

involved in fibrogenesis that synthesize collagen in the liver. Both cell types differ in location and physiology, the stellate cells lie within spaces of Disse whereas portal fibroblasts reside within the vicinity of portal tracts (5).

2.2.2.2. HEPATIC STELLATE CELLS

In the quiescent state, hepatic stellate cells generate primarily type IV collagen. During hepatic injury, inflammatory mediators, including both apoptotic and necrotic hepatocytes and paracrine stimuli from neighboring cell types (Endothelial cells, Kupffer cells, etc.) initiate the stellate cell activation. Subsequently, key cytokines are able to further stimulate the activated HSC causing the transformation into myofibroblasts.

The phenotypic switch induces besides collagen synthesis (type I and III) also cellular proliferation, loss of retinoid droplets, increased contractility, chemotaxis and the production of matrix-degrading enzymes and inflammatory signals. The high-density collagen deposition in the space of Disse leads to an increased and denser fibril-forming matrix. Sources producing collagenases with activity towards type I collagen are less developed as opposed to collagenases of the normal basement membrane collagen type IV.

The increasing scar matrix can therefore not be sufficiently degraded, which hinders the transport of solutes and growth factors across the interstitial space.

Irregular matrix deposition generally happens in damaged and inflamed areas of the parenchyma and imposes detrimental effects on the hepatocytes' differentiated cell function. Sinusoidal vascular resistance is enlarged by the tonic contraction of these myofibroblasts (14).

A recent study also indicates that paracrine signals released by activated HSCs may promote progenitor cell expansion, the outcome of which is either hepatic regeneration or promotion of hepatocarcinogenesis (16). Once hepatic homeostasis has restored, the activated HSCs either revert to quiescent phenotypes or are cleared by apoptosis. The cross-linking of collagen and the maturation of the hepatic scar, however, remain the determinants of hepatic fibrosis reversibility (15).

2.2.2.2. PORTAL FIBROBLASTS

Portal fibroblasts are thought to play a pivotal role in cholestatic liver diseases and ischemia (15). The cells are triggered by injury to portal tracts, resulting in excessive collagen deposition near ducts and ductules. Their rapid proliferation may engender biliary fibrosis to run an aggressive course. Furthermore, hepatic macrophages show divergent roles as matrix remodeling regulators. During fibrotic progression, macrophages promote fibrogenesis, whereas during fibrotic regression matrix degradation is accelerated (16).

2.2.2.3. REGENERATIVE NODULES

Cirrhosis is considered as an advanced stage of liver fibrosis, characterized by alterations of the lobular structure and the presence of regenerative nodules and vascular anastomoses. Several theories have been offered to elucidate the regenerative mechanism and the formation of fibrous septa, two critical events inherent to cirrhotic progression. Septa or sheetlike structures arise due to various causes. In the presence of steatosis, fat droplets merge to form fatty cysts, around which micromembranes develop.

Eventually the fat disappears from the cysts and the connective tissue framework condenses into septa. In addition, stress-induced fissures appear between areas of irregular distributed fat. Fine connective tissue membranes are deposited in these fissures and cumulate into straight septa (10).

Fibrotic membranes laid down around inflamed portal tracts, however, are more important during the septa-forming process, especially in the absence of steatosis. These connective tissue membranes radiate from the portal tracts into the parenchyma and converge afterwards to become septa. The septa development leads to a rearrangement of liver cell plates. Hepatocellular damage also contributes substantially to the septa formation, as irregular tissue stresses can evoke intralobular and periportal fissures. In these fissures, membranes aggregate

into septa. Furthermore, the lobular collapse following (extensive) necrosis causes central fields and portal tracts to become approximated and produces post-necrotic scar tissue (10).

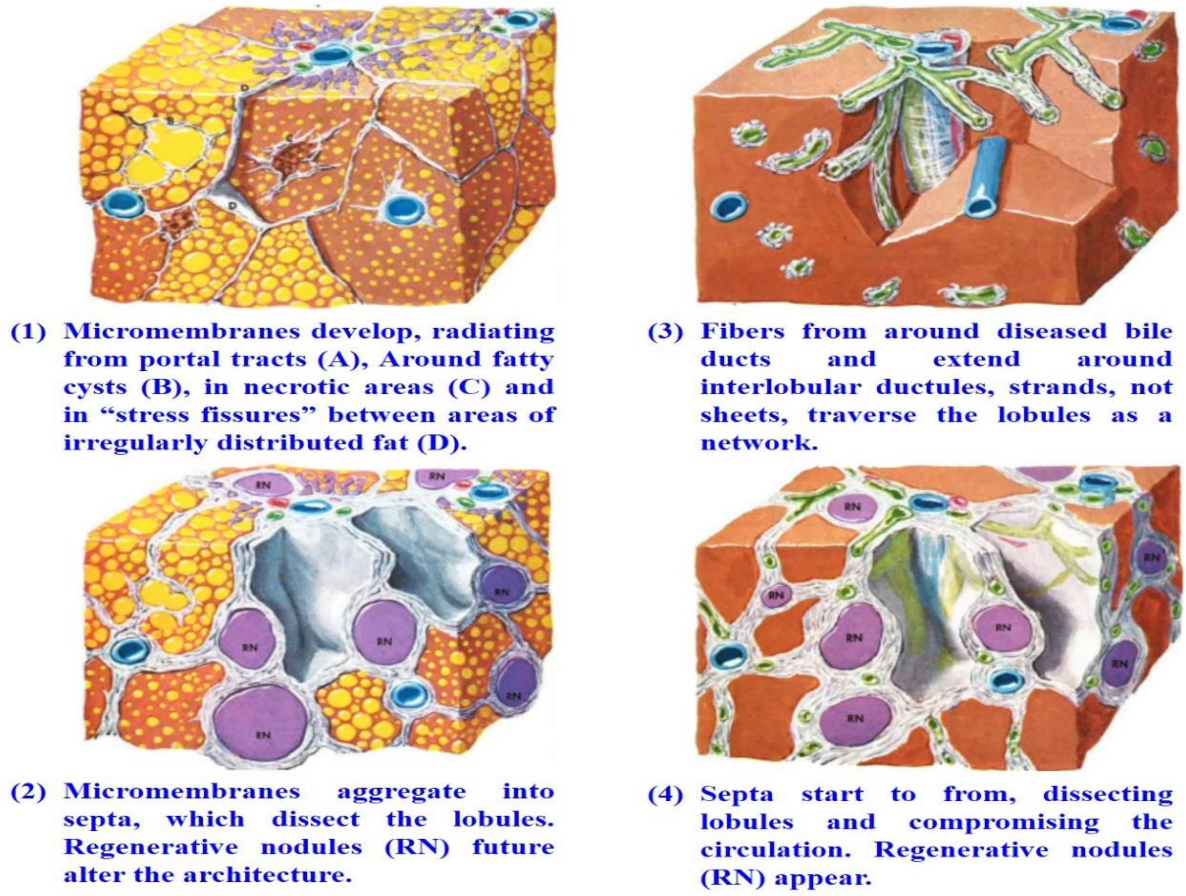


Fig. 8. Formation of Regenerative Nodules

The fibrous septa thus alter the lobular architecture and thereby perturb the hepatic blood flow. In chronic biliary diseases, fiber strands, and not the typical septa, are formed around the ducts. The accumulation of these strands does increase the extracellular matrix but without significantly disturbing the lobular

architecture. At a further stage, however, and mainly due to sustained inflammatory reactions, septa still arise from these fibers strands (10).

As a response to necrosis and the altered hepatic hemodynamics, regenerative processes take place. These lead to thickening and concentrical rearrangement of liver cell plates which have been separated from their natural environment due to fibrous septa. The plates' normal thickness of one cell increases to two cells. This regenerative effort combined with the localized proliferation of liver cells islands, isolated during necrosis, ensure the diffuse formation and progression of benign regenerative nodules (17).

2.2.2.4. PATHWAYS OF STELLATE CELL ACTIVATION

Stellate cell activation unfolds progressively in sequential stages; this paradigm provides a useful framework for defining fibrogenic events after liver injury. In particular, the initiation phase, which refers to early events that render the quiescent stellate cell responsive to a range of growth factors, remains an important focus.

Rapid induction of "-PDGF receptor, development of a contractile and fibrogenic phenotype, as well as modulation of growth factor signaling are the cardinal features of this early response.

Features of stellate cell activation can be distinguished between those that stimulate initiation and those that contribute to perpetuation. Initiation is provoked by soluble stimuli that include oxidant stress signals (Reactive oxygen intermediates), apoptotic bodies, lipopolysaccharide (LPS), and paracrine stimuli from neighboring cell types including hepatic macrophages (Kupffer cells), sinusoidal endothelium and hepatocytes. Perpetuation follows, characterized by a number of specific phenotypic changes including proliferation, contractility, fibrogenesis, altered matrix degradation, chemotaxis and inflammatory signaling.

Eventually the fat disappears from the cysts and the connective tissue framework condenses into septa. In addition, stress-induced fissures appear between areas of irregular distributed fat. Fine connective tissue membranes are deposited in these fissures and cumulate into straight septa Fibrotic membranes laid down around inflamed portal tracts, however, are more important during the septa-forming process, especially in the absence of steatosis.

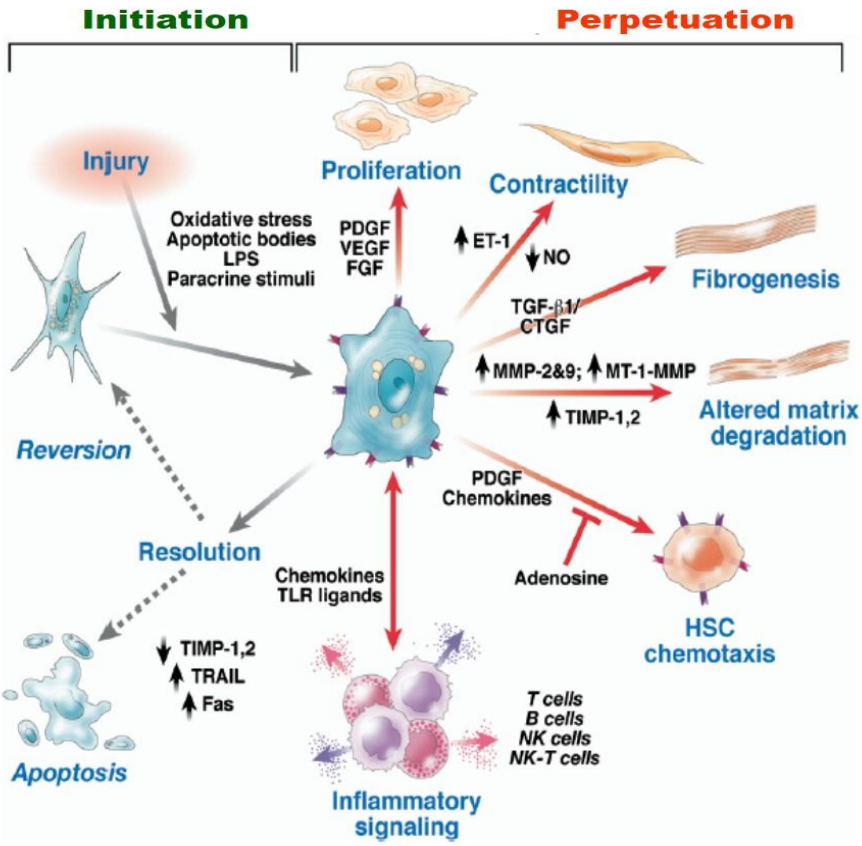


Fig. 9. Pathway of hepatic stellate cell activation

These connective tissue membranes radiate from the portal tracts into the parenchyma and converge afterwards to become septa. The septa development leads to a rearrangement of liver cell plates.

Hepatocellular damage also contributes substantially to the septa formation, as irregular tissue stresses can evoke intralobular and periportal fissures. In these fissures, membranes aggregate into septa. Furthermore, the lobular collapse following (Extensive) necrosis causes central fields and portal tracts to become

approximated and produces post-necrotic scar tissue. The fibrous septa thus alter the lobular architecture and thereby perturb the hepatic blood flow.

In chronic biliary diseases, fiber strands, and not the typical septa, are formed around the ducts. The accumulation of these strands does increase the extracellular matrix but without significantly disturbing the lobular architecture. At a further stage, however, and mainly due to sustained inflammatory reactions, septa still arise from these fibers strands. As a response to necrosis and the altered hepatic hemodynamics, regenerative processes take place. These lead to thickening and concentrical rearrangement of liver cell plates which have been separated from their natural environment due to fibrous septa.

This regenerative effort combined with the localized proliferation of liver cells Islands, isolated during necrosis, ensure the diffuse formation and progression of benign regenerative nodules. The growing nodules, in turn, contribute further to the septa condensation by compression of the adjacent tissue. The normal lobular architecture is thereby replaced by structurally abnormal nodules.

In diseases of intrahepatic bile ducts, nodular conversion is usually not induced until the liver is extremely fibrotic. These cholestatic diseases are more often characterized by exaggerated proliferation of ductules to provide an alternative route for the obstructed bile.

2.2.2.5. MORPHOLOGY OF CIRRHOSIS

Cirrhosis can be subdivided, based on its morphology, into micronodular or macronodular forms. Micronodular cirrhosis implies that almost all the regenerative nodules are less than 3mm in diameter (9). It most commonly originates from diseases in which a hepatotoxic agent or metabolic disorder uniformly affects the lobules. For instance, high-dose ethanol exposure causes primarily the deposition of connective tissue septa along sinusoids, linking portal tracts to central veins. When nearly all portal tracts and central veins are connected by septa, the fibrous tissue strongly constrains the enlarging nodules. Micronodules barely contain portal tracts or terminal hepatic veins.

Cirrhotic macronodules, on the other hand, may comprise residual portal structures and central veins, which are not bound by septa. Its diameter varies notably and ranges from 3mm to several centimeters. Macronodular cirrhosis is usually due to viral hepatitis and arises after continued massive collapse of cirrhotic parenchyma, promoting accentuated regeneration (10). Although regenerative nodules are benign, it is not uncommon that some progress along a carcinogenic pathway to become malignant nodules or hepatocellular carcinoma (17).

2.2.2.6. HEMODYNAMIC ALTERATIONS

Additional to the complex molecular processes involved in fibrogenesis (interacting cells, fibrogenic mediators, etc.) and the formation of regenerative nodules, modifications to the angioarchitecture are also considered as a central aspect in the pathological pathway to cirrhosis. These changes, including sinusoidal remodeling, angiogenesis and the development of intrahepatic shunts, increase the intrahepatic vascular resistance leading to various complications. Moreover, the degraded sinusoids hamper the metabolic exchange between sinusoids and hepatocytes, which may progress to life-threatening liver failure.

2.2.2.6.1. SINUSOIDAL CAPILLARIZATION

Sinusoidal capillarization induces microcirculatory distortions in the liver. It comprises collagenization of the space of Disse, deposition of basement membranes and alterations of fenestrae is accompanied by a loss of hepatocyte microvilli.

The aggregation of fibrous connective tissue, due to fibrogenesis, hampers the diffusion of blood solutes across the extravascular space of Disse during the metabolic exchange between sinusoids and hepatocytes. Moreover, the excessive

fibrotic tissue in the space of Disse combined with the hepatic stellate cells' tonic contraction, leads to narrowing of sinusoids and hence increases the sinusoidal vascular resistance which, in turn, impedes sinusoidal perfusion (5).

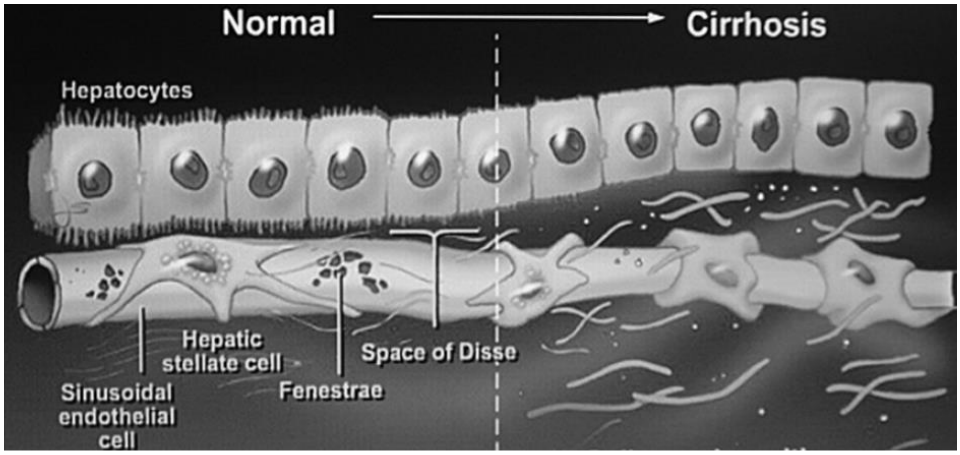


Fig. 10. Collagen deposition and sinusoidal constriction in cirrhosis.

The formation of basement membranes near the endothelium and epithelium, acts as an additional barrier to restrict access to the extravascular space. In addition, the number and size of fenestrae progressively decreases in cirrhotic livers. The fenestrated sinusoids are therefore transformed into continuous and more rigid capillaries, which contribute further to the increasing intrahepatic vascular resistance and the subsequent development of portal hypertension.

The limited permeability of the sinusoids deprives the hepatocytes of nutrients and the ability to perform vital metabolic functions. Sinusoidal

capillarization hence contributes to liver failure, regardless of the metabolic capacity of hepatocytes (18, 19 & 20).

2.2.2.6.2. ANGIOGENESIS AND INTRAHEPATIC SHUNTS

The anomalies frequently observed in cirrhotic livers, are angiogenesis and the presence of intrahepatic shunts. Both vascular abnormalities predominate along regions of active inflammation and fibrous septa. In these hypoxic conditions, the transcription of the vascular endothelial growth factor (VEGF) is substantially up regulated by hepatic stellate cells in order to stimulate angiogenesis. It is likely that the sustained hypoxic state in fibrotic areas thus gives rise to the formation of new blood vessels or the reopening of preformed vessels, to countervail the inadequate blood supply and to restore the intrahepatic blood circulation (21 & 22).

In post-necrotic scars or during the septa formation, liver sinusoids get entrapped within connective tissue. After parenchymal collapse, portal and central field's approximate and adjacent septa eventually merge to form fibrous bridges between portal tracts and central veins. The bridging separates the sinusoids entirely from the parenchyma. While some of the trapped sinusoids are obliterated due to the fibrous septa, others are transformed into widened porto-hepatic venous anastomoses (or internal Eck's fistulae). Blood, guided into those low hindrance pathways, bypasses the liver cells, and is shunted directly into central veins (5).

The intrahepatic shunts thus impoverish the surviving parenchyma of nutritive blood supply, and thereby contribute to hepatocellular necrosis (10). With the collapse of perivenous tissue during necrosis, portal tracts and central fields become approximated.

The accompanying fibrotic processes often obliterate the smaller portal veins, while hepatic arteries are less subjected to the compression. As a consequence, the HABR compensatory mechanism increases the part of hepatic blood coming from the artery (23). Arteriovenous anastomoses, developed in septa connecting portal veins and hepatic arteries, partially redistribute the elevated arterial pressure to the portal vein and, as such, contribute to portal hypertension (10).

2.2.2.6.3. CIRRHOTIC ANGIOARCHITECTURE

The normal lobular angioarchitecture almost completely disappears in a cirrhotic liver due to persistent damage to portal fields. While chronic hepatitis lacks the presence of regenerative nodules, spatial disarrangements and alterations of the angioarchitecture already appear in this earlier stage of the process toward cirrhosis. Fibrous bridges, connecting an enlarged portal tract and hepatic vein, contain numerous tortuous and intermingled blood vessels. Various portal veins run parallel, of which only a few (asterisks) extend outwards into the parenchyma

to nourish liver cells. Those rather small veins resemble point-like inflow sources and provide the nutrition for liver cells to regenerate. When regenerative nodules become completely isolated from their portal blood supply, hepatic arteries are assumed to contribute to the maintenance of the nodules (5). Another hypothesis, however, suggests that angiogenic pathways are activated within regenerative nodules to promote the formation of new blood vessel (10).

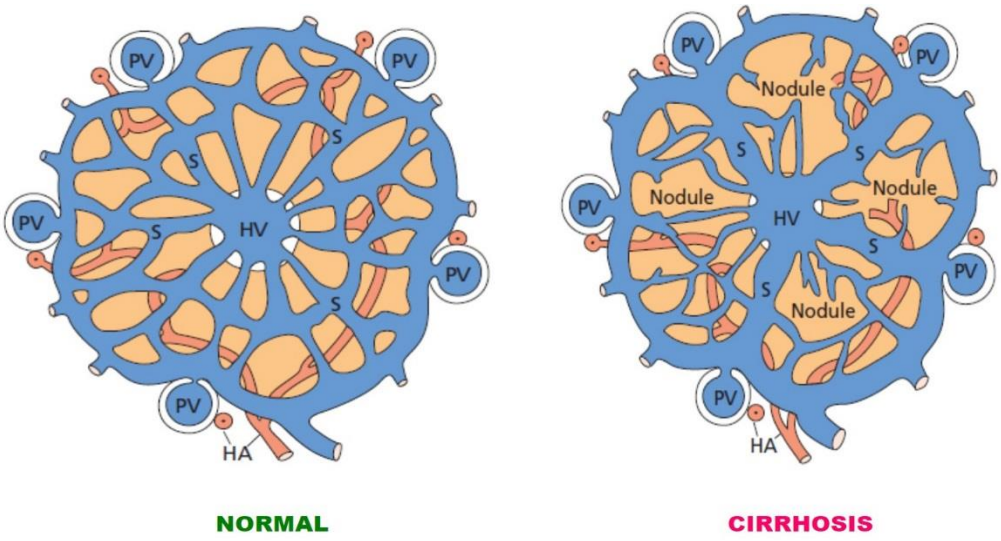


Fig. 11. Formation of Cirrhotic Angioarchitecture

2.2.3. CLIICAL FEATURE COMPLICATIONS

Based on clinical outcomes, cirrhosis can be described as either compensated or decompensated. Decompensation implies the manifestation of clinically evident complications resulting from either portal hypertension or liver deficiency (jaundice etc.).

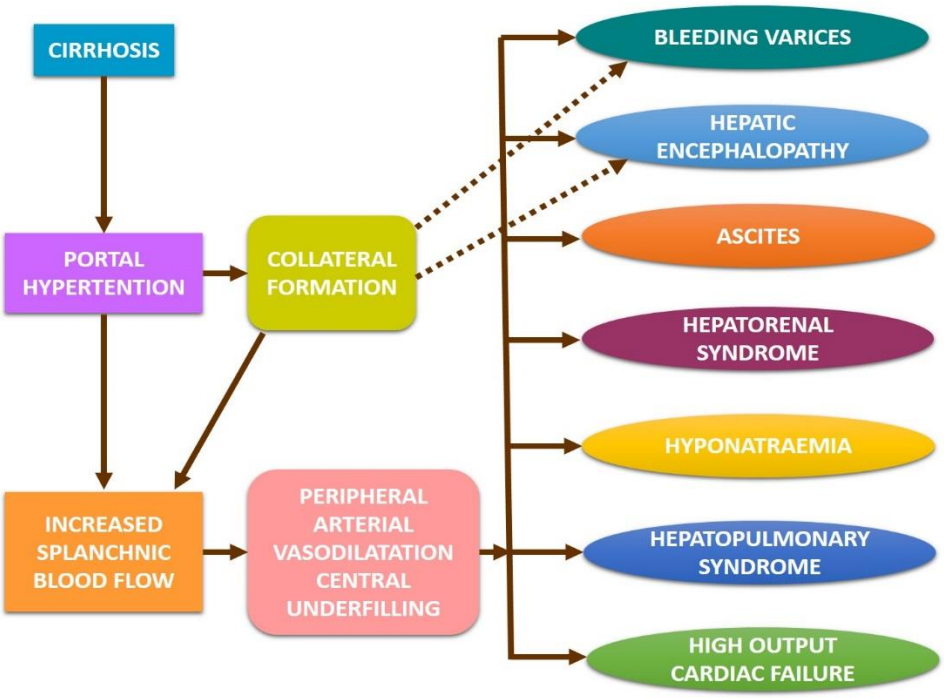


Fig.12. Complications of Cirrhosis

Compensated cirrhosis, on the other hand, is non-symptomatic, as the liver is able to compensate for the incurred liver damage. However, it can progress towards decompensation (24).

2.2.3.1. PORTAL HYPERTENSION

All forms of cirrhosis lead to portal hypertension and the primary event is obstruction to portal blood flow. Portal venous blood is diverted into collateral channels and some bypasses the liver cells and is shunted directly into the hepatic venous radicles in the fibrous septa.

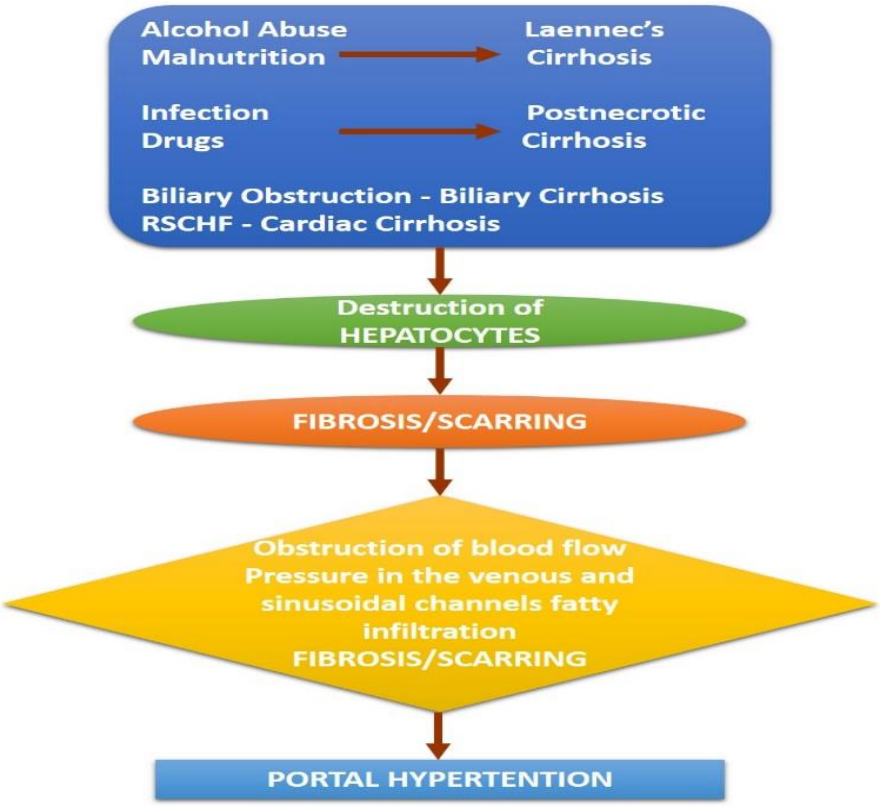


Fig.13. Formation of Portal Hypertension

These portohepatic anastomoses develop from pre - existing sinusoids e nclosed in the septa. Even larger portohepatic venous anastomoses are found in the cirrhotic liver. About one - third of the total blood flow perfusing the cirrhotic liver may bypass sinusoids, and hence functioning liver tissue, through these channels.

The obstruction to portal flow is partially due to nodules which compress hepatic venous radicles. This would lead to a postsinusoidal portal hypertension. However, in cirrhosis, the wedged hepatic venous (sinusoidal) and main portal pressures are virtually identical and the stasis must extend to the portal inflow

vessels. Sinusoids probably provide the greatest resistance to flow. Changes in the space of Disse, particularly collagenization, result in sinusoidal narrowing and this may be particularly important in the alcoholic. Hepatocyte swelling in the alcoholic may also reduce sinusoidal flow.

Portal hypertension may arise in cirrhotic livers as a consequence of the increased intrahepatic vascular resistance (regenerative nodules and fibrous tissue) coupled with an increased portal blood flow (hyperdynamic circulation). Due to the distorted angioarchitecture and abnormal hemodynamics, the blood pressure in the portal venous system, normally varying between 5 and 10 mmHg, then exceeds a value of 10 mmHg (24 & 25). The hypertension can be linked to most of the clinical complications of cirrhosis.

2.2.3.2. ASCITES

Ascites is the accumulation of excessive fluid within the peritoneal cavity. It is most frequently encountered in patients with cirrhosis and other forms of severe liver disease, although a number of other disorders may lead to either transudative or exudative ascites.

2.2.2. PATHOGENESIS

The accumulation of ascitic fluid represents a state of total body water and sodium excess, but the event that initiates this imbalance is unclear. Three theories have been proposed.

The "Underfilling" theory suggests that the primary abnormality is inappropriate sequestration of fluid within the splanchnic vascular bed due to portal hypertension and a consequent decrease in effective circulating blood volume. According to this theory, an apparent decrease in intravascular volume (underfilling) is sensed by the kidney, which responds by retaining salt and water.

The "Overflow" theory suggests that the primary abnormality is inappropriate renal retention of salt and water in the absence of volume depletion.

A third, more attractive theory, the peripheral arterial vasodilatation hypothesis, may unify the earlier theories. It accounts for the constellation of arterial hypotension and increased cardiac output in association with high levels of vasoconstrictor substances that are routinely found in patients with cirrhosis and ascites. Again, sodium retention is considered secondary to arterial vascular underfilling which is the result of a disproportionate increase of the vascular compartment due to arteriolar vasodilation rather than from decreased intravascular volume.

According to this theory, portal hypertension results in splanchnic arteriolar vasodilation, mediated by nitric oxide, and leads to underfilling of the arterial vascular space and baroreceptor-mediated stimulation of reninangiotensin, sympathetic output, and antidiuretic hormone release. Regardless of the initiating event, a number of factors contribute to accumulation of fluid in the abdominal cavity. Elevated levels of serum epinephrine and norepinephrine have been well documented. Increased central sympathetic outflow is found in patients with cirrhosis and ascites but not in those with cirrhosis alone. Increased sympathetic output results in diminished natriuresis by activation of the renin-angiotensin system and diminished sensitivity to atrial natriuretic peptide.

Portal hypertension plays an important role in the formation of ascites by raising hydrostatic pressure within the splanchnic capillary bed. Hypoalbuminemia and reduced plasma oncotic pressure also favor the extravasation of fluid from plasma to the peritoneal cavity. Thus ascites is infrequent in patients with cirrhosis unless both portal hypertension and hypoalbuminemia are present. Hepatic lymph may weep freely from the surface of the cirrhotic liver due to distortion and obstruction of hepatic sinusoids and lymphatics and contribute to ascites formation.

Renal factors also play an important role in perpetuating ascites. Patients with ascites fail to excrete a water load in a normal fashion. They have increased

renal sodium reabsorption in proximal and distal tubules, the latter largely due to increased plasma renin activity and secondary hyperaldosteronism. Insensitivity to circulating atrial natriuretic peptide, often present in elevated concentrations in patients with cirrhosis and ascites, may be an important contributory factor in many patients. Renal vasoconstriction, perhaps resulting from increased serum prostaglandin or catecholamine levels, may also contribute to sodium retention. Recently a role for endothelin, a potent vasoconstrictor peptide, has been proposed. While elevated levels have been reported by some, this has not been observed by others (5).

2.2.3. CLINICAL FEATURES AND DIAGNOSIS

Usually ascites is first noticed by the patient because of increasing abdominal girth. More pronounced accumulation of fluid may cause shortness of breath because of elevation of the diaphragm. When peritoneal fluid accumulat ion exceeds 500 mL, ascites may be demonstrated on physical examination by the presence of shifting dullness, a fluid wave, or bulging flanks. Ultrasound examination, preferably with a Doppler study, can detect smaller quantities of ascites.

2.2.3.1. VARICES (COLLATERAL CIRCULATION)

Extensive portal – systemic venous communications develop in order to decompress the high – pressure portal venous system. Maintenance of portal hypertension after the collateral are formed, is attributed to a resultant increase in splanchnic blood flow.

2.2.3.1.1. MAJOR SITES OF COLLATERALS

- Oesophageal and gastric varices (Left gastric vein and short gastric vein join with intercostal, diaphragragmatic, oesophageal and azygos veins of the caval system).
- Heamorrhoids (Superior haemorrhoidal vein of the portal system to middle and inferior haemorrhoidal veins of the caval system).
- Caput medusa (Remnants of the umbilical circulation of the foetus present in the falciform ligament may form a large paraumbilical vein).
- Other sites of anastomoses are retroperitoneal vein, lumber vein, omental veins and veins over bare area of the liver.

2.2.3.1.2. VARICEAL BLEEDING

Variceal bleeding occurs when portal venous pressure is more than 12 mm Hg. Mostly bleeding arises from oesophageal varices within 3 to 5 cm of the oesophagogastric junction or from gastric varices.

2.2.3.1.3. FACTORS PREDISPOSING TO BLEEDING

- Large varices
- Endoscopic variceal stigma (red spots and red stripes)
- High portal pressure
- Liver failure
- Drugs (NSAIDs)
- Tence ascites.

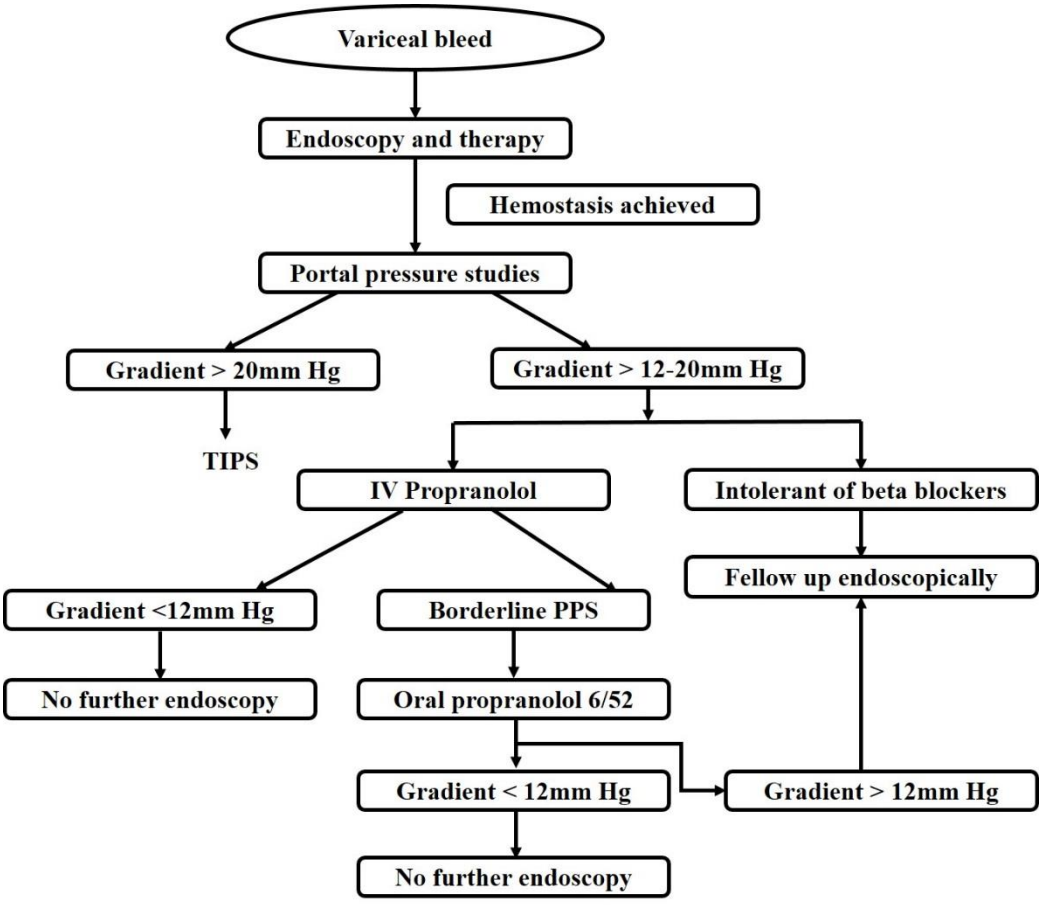


Fig. 14. Management of Variceal Bleed

2.2.4. HEPATIC ENCEPHALOPATHY

The hyperdynamic circulation is probably caused by an overproduction of nitric oxide, a vasodilator molecule, in the extrahepatic blood flow. The NO overproduction is promoted by the increased intestinal permeability of bacterial endotoxins. Due to the NO molecule, the vascular resistance in the splanchnic and systemic circulations substantially decreases, leading to an increased splanchnic blood flow (and portal blood flow) and elevated cardiac output.

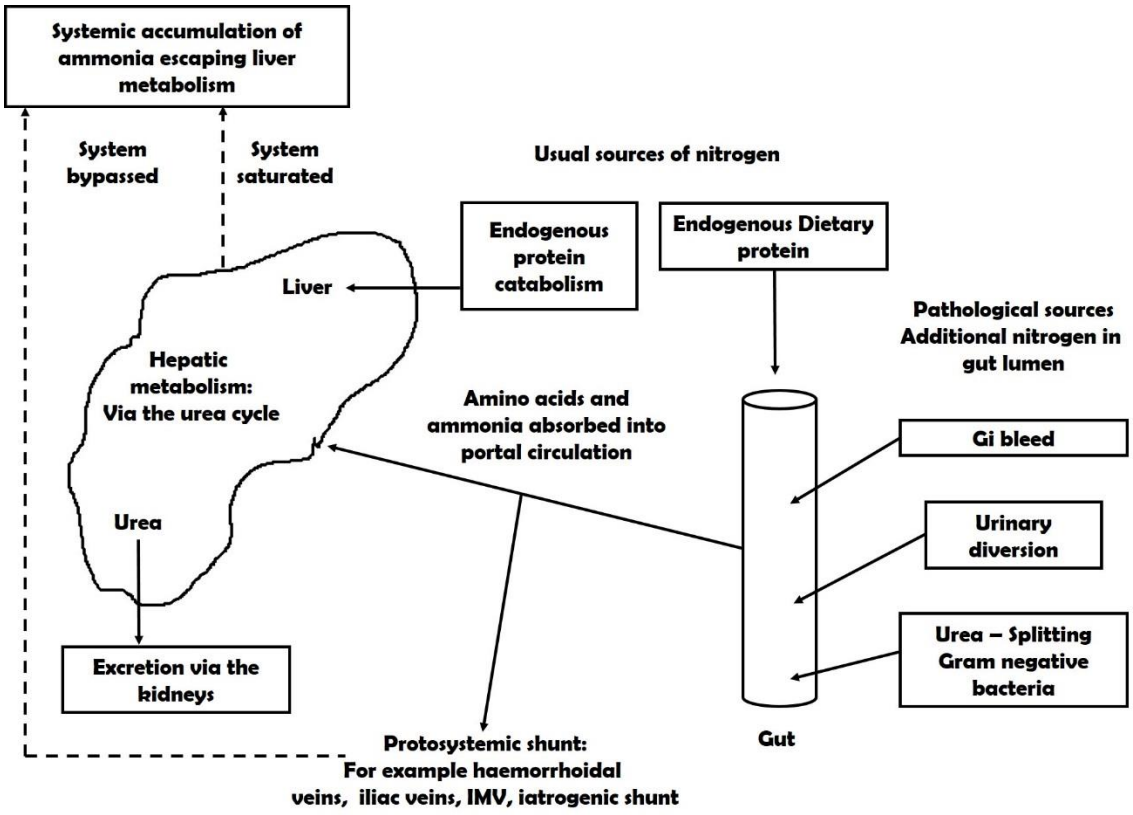


Fig.15. Mechanisms of Hepatic Encephalopathy

In addition, portal hypertension results in the development of portosystemic collaterals. These alternative channels bypass the liver and guide a part of the increased portal blood flow directly into the systemic venous system without purification. Both hepatocellular failure and portosystemic shunting play a pivotal role in hepatic encephalopathy (26).

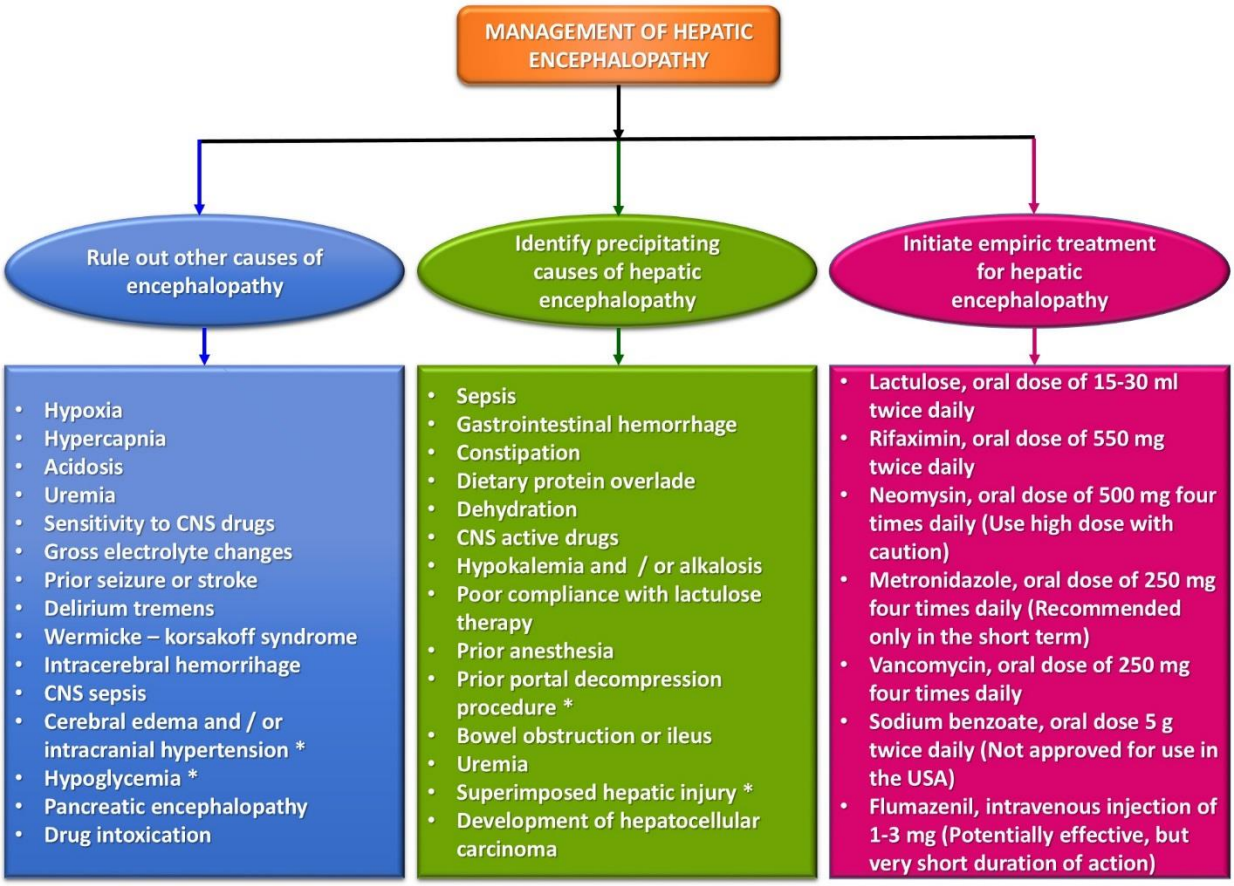


Fig.16. Management of Hepatic Encephalopathy

2.2.5. SPONTANEOUS BACTERIAL PERITONITIS

It is defined as infected ascetic fluid in the absence of recognizable secondary cause of peritonitis. It is associated with an ascetic protein of <1gm/dL. Spontaneous Bacterial Peritonitis (SBP) can occur in upto 30% of individuals.

2.2.5.1. ORGANISMS

Coliforms, Streptococci, Camphylobacter; uaually infection is blood – borne. Ascitic fluid infection can also be due to *staph*. *Aureus* and E*nterococcus*. *E. coli* infection is more common.

2.2.5.2. MECHANISM

Bacterial translocation from the gut through mesenteric node. Culture are more likely to be positive when 10 ml of ascetic fluid is inoculated into two culture bottles at the bed side. If more than two organisms are identified in culture, secondary bacterial peritonitis due to preformation should be considered.

2.2.6. HEPATORENAL SYNDROME

The haemodynamic alteration in kidneys are as a result of decreased effective blood volume and increased sympathetic tone. Increased intra – abdominal and renal venous pressure and alteration of balance between vasoactive humoral agents

such as renin – angiotensin, prostaglandins, theromboxanes, kinins, endotoxins, and renal kallikrein may play a role.

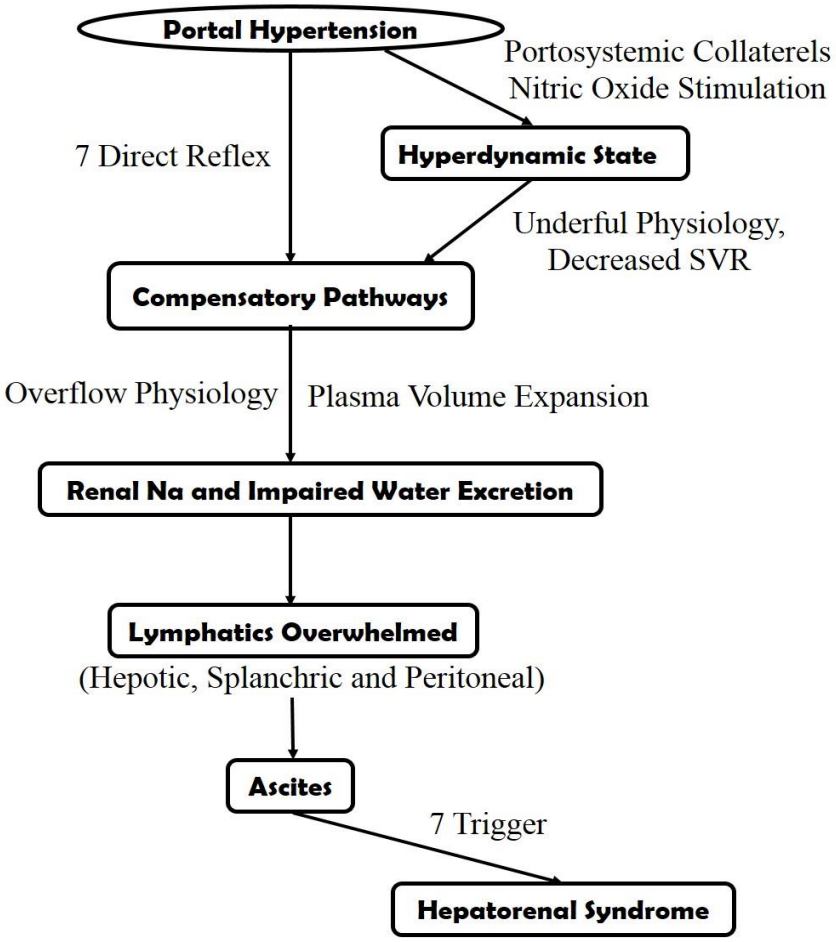


Fig.17. Hepatorenal Syndrome

Involvement of endothelin – 1and 3 has been implicated in hepatorenal syndrome. Role of nitric oxide has also been suggested as one of the mechanisms. The kidneys are anatomically, histologically and functionally normal.

Following six criterias must be present to confirm diagnosis;

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg %.
- Absence of other causes of renal failure as evidenced by proteinuria > 500 mg/dL, urine RBC> 50/HPF and abnormal renal USG.
- No evidence of treatment with nephrotoxic drugs/vasodilators.
- Absence of shock
- Absence of sustained improvement of renal function following at least 2 days of diuretic withdrawal and volume expansion with albumin.

2.2.7. HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome is characterised by

- Advanced Chronic Liver Disease
- Arterial Hypoxaemia (Decreased Pao_2)
- Intra – Pulmonary Vasodilatation
- No Primary Cardio – Pulmonary Disorder (26).

2.2.8. OTHER COMPLICATIONS

- Hyponatraemia
- High Output Cardiac Failure
- Peripheral Arterial Vasodilatation
- Central Under filling Collateral Formation

- Increased Splanchnic Blood Flow

2.3. LIPID METABOLISMS

2.3.1. THE ADIPOSE TISSUE

Triglycerides comprise around 95% of dietary lipids and can be stored within the specialised storage organ adipose tissue, or within other organs, principally liver and muscle. Lipids play essential roles in energy storage, vitamin absorption, cellular membrane maintenance and cellular signalling.

The fatty acid content of the body originates either from exogenous dietary sources or from endogenous synthesis. Circulating lipoprotein and chylomicron-bound lipids increase following an intake of lipid containing foodstuffs. Lipoprotein lipase breaks down the triacylglycerol (triglyceride) from these circulating complexes, releasing non-esterified fatty acids (NEFA) which are taken up into adipocytes, where they are esterified into triglyceride and stored.

The high energy density of triglyceride (9 kcal/g) means that it is a more efficient energy store than protein (4 kcal/kg) or carbohydrates (3.75 kcal/kg). During a period of energy demand which is greater than exogenous supply, the stored triglyceride is hydrolysed by hormone-sensitive lipase and re-mobilised

back into the circulation as NEFA. These opposing actions of lipid storage and lipolysis are under strict hormonal control.

The hormones adrenaline, adrenocorticotropic hormone (ACTH) and glucagon promote lipolysis, whereas insulin promotes lipid storage and esterification. This hormonal profile is ultimately influenced by metabolic need, metabolic reserves and stress.

Traditionally adipose tissue was considered as being merely the major storage organ for triglyceride, and little significance was attributed to ectopic lipid storage in liver or muscle. This has radically changed over the past decade or so.

Adipose tissue has emerged as a major endocrine organ, muscle lipids have been implicated in insulin resistance and hepatic lipid in altering local and whole-body metabolic and inflammatory status.

Adipose tissue secretes over 100 differing factors including adipokines, steroid hormones, fatty acids, and prostaglandins. With the exception of adiponectin, these factors are all released in greater amounts with increasing adipose tissue volume. Adiponectin, a key regulatory factor, promotes insulin sensitivity and β-oxidation.

About 20% of the total body weight of a normal young adult constituted by adipose tissue. There is almost no limit to the extent to which this stroke of adipose tissue can be increased. Thus in obese individual weighing 140 Kg more than 50% of the body weight is represented by adipose tissue.

Adipose tissue is found subcutaneously over the entire body in man, with some extra deposits in the areas of the buttocks and breasts. There are large deposits of adipose tissue in the mesentery, some around the kidneys and the heart. In addition to its physiologic role as a stroke of calories, adipose tissue plays a structural role for example in cushioning of viscera and as an insulating layer reducing the rates of loss of body heat.

The mature adipose tissue cell (adipocyte) consists of a large structureless droplet of lipid surrounded by a very thin rim of cytoplasm (27). For many years adipose tissue was considered to be relatively inert tissue. The mass of the adipose tissue in sustaining the body during starving is evident even to the casual observer.

2.3.2. LIPID CHEMISTRY

A lipid is a fat like substance that may not actually be related to fatty acids although occasionally the terms lipids and lipoids are used synonymously. Lipids are waxy, greasy, and oily compounds of the body. It is hydrophobic in nature. In the body fat serves as an efficient source of energy, except for the brain. Caloric

value of fat is 9KCL/gm. Combination of fat and protein (lipoprotein) are important cellular constituents. They form important dietary constituents as an account of their high calorific value and the fat soluble vitamins and the essential fatty acids contained in them (28 & 29).

2.3.3. CHEMICAL CLASSIFICATION OF PLASMA LIPIDS

- Simple lipids
- Fatty acids
- Steroids
- Cholesterol
- Steroid hormones
- Vitamin D
- Carotene
- Vitamin A,E,K
- Prostaglandins
- Complex lipids
- Triglyceride
- Cholesterol ester
- Phospholipids
- Sphingolipids
- Waxes

2.3.4. FUNCTIONS

In general lipids are important as;

- Structure of cell membranes, because lipids are integral part of all cell membranes.

- As ready source of energy, because lipids supply over half of the energy utilized in basal metabolism.
- A structure of sex hormones.
- Thermal blanket, because their presence in subcutaneous tissue insulates the body against heat loss.

2.5.5. FATTY ACIDS

They are carboxylic acids obtained from the hydrolysis of mainly glycerol and cholesterol. They contain on even number of carbon atoms and are straight chain derivatives. The chain may be saturated (containing no double bonds) or unsaturated (containing one or more double bonds). The main saturated fatty acids in the plasma are butyric, caproic, palmitic and stearic acid.

Unsaturated fatty acids are again subdivided into:

- Monounsaturated (monoethenoid, monoenoic acids).
- Poly unsaturated (Polyethenoid, polyenoic acids).
- Eicosinoids: Comprise prostaglandins, leucotriens, prostaglandins and
- thrombaxane.

Many other fatty acids have been detected in the biologic material Normal Values: 250-400 mg/dl. Free fatty acids are immediately available energy source and provides much of the energy requirements of the body (28 & 29).

2.3.5. CHOLESTEROL

It was first described towards the end of 18th century by French chemist De Fourerol. It is distributed in all cells of the body but particularly in nervous tissue. Cholesterol is the most important compound of those classed as sterols. It is a precursor of bile acids, the steroid hormones and Vitamin D. With fatty acids, it forms waxes. It is a stable white crystalline substance insoluble in water but readily soluble in chloroform, ether, alcohol, and other fat solvents. The sterol is present in high amounts in nervous tissue (2%), liver (0.3%), skin (0.3%) and intestine (0.2%) and certain endocrine glands (27 & 29).

The relative high content of the cholesterol in skin may be related to vitamin D formation and that in adrenals to steroid hormones synthesis. Much attention being directed to cholesterol at present time, not only because of its close relationship to other steroids in the body, but also because cholesterol is involved in certain degenerative changes in the arterial well known as atherosclerosis.

Normal Values: Range from 160-240 mg/dl.

2.3.6. TRIGLYCERIDES (TRIACYLGLYCEROLS)

The triacylglycerols or so called neutral fats, are esters of the alcohol glycerol and fatty acids. According to the current standardized, terminology of the International Union of Pure and Applied Chemistry (IPAUC) and the International Union of Biochemistry (IUB), the monoglycerides, diglycerides and triglycetides are to be designated monoacyl, diacyl and triacylglycerols respectively.

On hydrolysis triglycerides may yield 3 molecules of fatty acid, and 1 molecule of glycerol when it is boiled with an alkali such as NAOH or KOH. Then glycerol and Na and K salt of fatty acids (soap) are formed (27 & 29). Aggregates of triglycerides (80%), phospholipids (7%) and cholesterol (9%) are coated with lipoproteins to produce particles called chylomicrons.

Normal values: 40-150 mg%.

2.3.7. PHOSPHOLIPIDS

Phospholipids are complex lipids, resembling triglycerides, but containing phosphate and a nitrogenous base. The major phospholipids in plasma are lecithin and sphingomyelin. The phosphate and nitrogenous base are water-soluble. Lipids are carried in the plasma in the form of lipoprotein complexes. These complexes of

lipid and protein impart solubility to the otherwise insoluble lipids, and all lipids enter and travel through the blood stream as lipid-protein complexes.

2.3.8. STRUCTURE OF A LIPOPROTEIN PARTICLE

The lipoproteins are globular particles of high molecular weight that transports non-polar lipids through the plasma. Each lipoprotein particle contains a hydrophobic core of triglyceride and cholesterol ester, surrounded by a coat containing polar phospholipids, free cholesterol and apoproteins 8 that stabilize the lipoprotein particle so that it can remain in solution form in the plasma. The apoprotein decides the role of a lipoprotein like binding to specific enzyme or onto cell membrane, thus directing the lipoprotein to the site of metabolism.

Schulz (1897) and Machebouf (1929) suspected the role of lipid protein complexes in maintaining the lipids in solution in plasma. Application of new physical methods for protein separation including electrophoresis and centrifugation expedited progress in lipoprotein chemistry. Tiselius et al in 1941 reported the existence of two lipoprotein classes, seperable by moving boundary electrophoresis. These were alpha and beta lipoproteins. After another decade pre betalipoprotein was identified by zonal electrophoresis.

2.3.9. MAJOR CLASSES OF APOLIPOPROTEINS

- Apolipoprotein A (A I,A II)
- Apolipoprotein B(B48,B100)
- Apolipoprotein C(CII,III,IV)
- Apolipoprotein E(E2,E3,E4)

Apoproteins provide structural stability to lipoproteins (30) such as solubilizing lipids, activating enzymes, and initiating receptor mediated clearance of lipoproteins.

Lipoprotein class	Density (g/mL)	Diameter (nm)	Protein % of dry wt	Phospholipid %	Triacylglycerol
HDL	1.063 – 1.21	5 - 15	33	29	8
LDL	1.019 – 1.063	18 – 28	25	21	4
IDL	1.006 – 1.019	25 – 50	18	22	31
VLDL	0.95 – 1.006	30 – 80	10	18	50
Chylomicrons	<0.95	100 – 500	1 - 2	7	84

Table. 1. Major Classes of Lipoproteins

Measurement of apoprotein A levels may predict patients with increased risk of coronary artery disease better than HDL levels. Research has shown that

apolipoprotein A appears to be an independent risk factor in the development of cardiovascular disease.

There are two major proteins in the apoprotein B family. The smaller one is apoprotein B-48 which is the major structural protein of chylomicrons and is responsible for the secretion of the same (30). The larger form is apoprotein B-100, the major structural protein of VLDL (31) and LDL. It is essential for the secretion of VLDL from liver and as a ligand for removal of LDL by LDL receptor. It may be elevated in some patients with coronary heart disease and normal cholesterol levels.

Apoprotein C is found in all lipoproteins. They regulate the activity of lipoprotien lipase and inhibit removal of chylomicrons and VLDL by liver. Apoprotein C2 activates the enzyme. Its absence prevents normal lipolysis and causes hypertriglyceridemia. Apoprotein C3 retards catabolism of VLDL and chylomicrons (30).

Apolipoprotein E also is present in VLDL and chylomicrons. They are required for normal catabolism of remnants by a specific receptor on the liver that recognizes Apoprotein E. There are three forms of apoprotein E1, E2, E3, E4 (30).

2.3.10. NORMAL LIPOPROTEIN METABOLISM

Chylomicrons are formed from dietary fats and cholesterol absorbed in the intestine. They are secreted into the lymph, pass through the thoracic duct and eventually enter the systemic circulation. As chylomicrons enter capillaries, they come into contact with an enzyme, lipoprotein lipase, located on the surface of endothelial cells particularly in adipose tissue and muscle. Lipoprotein lipase needs insulin for maintenance of adequate tissue levels. The interaction of chylomicrons and lipoprotein lipase results in hydrolysis of triglyceride to fatty acids and glycerol.

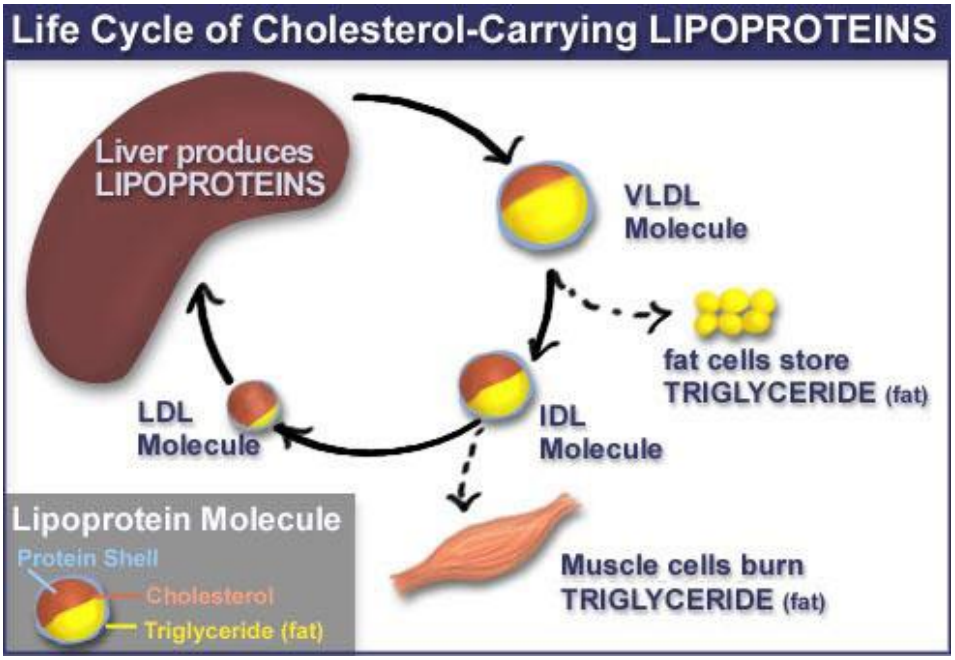


Fig.18. Cholesterol – Carrying Lipoproteines

2.3.11. OVERVIEW OF HEPATIC FATTY ACID METABOLISM IN HEALTH

The liver is the key organ in determining the metabolism and distribution of fatty acids. It is the source of endogenous synthesis and degrades or interconverts exogenous fatty acids. The resultant fatty acids may either be stored in the liver itself, or exported to adipose tissue and muscle. Hepatic fatty acid metabolism is dynamic with triglyceride turnover occurring every 2 days.

Circulating fatty acids are either bound to lipoproteins or albumin. Lipoprotein-bound lipids, which include chylomicron complexes, are internalised into cells following the formation of a specific apolipoprotein-receptor complex. Dietary medium-chain triglycerides enter the portal circulation directly, whereas longer chain fatty acids enter the vascular circulation complexed with chylomicrons via the lymphatic system and the thoracic duct.

Historically it was believed that in contrast to lipid-lipoprotein complexes, the albumin bound NEFAs are internalised into cells via simple and direct penetration of the plasma membrane. The recently discovered cluster differentiation protein 36 (CD 36) forms a pathway for hepatic fatty acid uptake which is upregulated by insulin and experimental models of NAFLD (Ge, Zhou et al. 2010; Larter, Chitturi et al. 2010). As a result NEFAs are the key fatty acid

source for the liver with an uptake that is directly proportional to its delivery rate (Havel, Kane et al. 1970) and potentially increased by insulin resistance and NAFLD. The concentration of circulating NEFAs is dependent on their release from adipocytes and myocytes. This is regulated by hormone sensitive lipase, 20 which is stimulated by adrenaline, and inhibited by insulin (Qureshi and Abrams 2007).

Insulin also acts to reduce circulating glucose concentrations by promoting its tissue uptake. Insulin resistance however results in increased circulating concentrations of insulin, and the principal hepatic fatty acid substrates, namely glucose and NEFA. As a result insulin resistance promotes hepatic lipogenesis as will be further discussed later. Intra-hepatic fatty acids are cytotoxic (Gibbons, Wiggins et al. 2004) and so are further metabolised by three potential and separate processes: either beta-oxidation, VLDL synthesis or intra-hepatic storage as triglycerides. In the presence of high energy demand, intra-hepatic fatty acids undergo oxidation to generate energy in the form of ATP. If there is a low energy demand then intra-hepatic fatty acids are esterified into triglycerides and either stored in the hepatocyte or exported as VLDL.

2.3.11.1. OXIDATION

Within the mitochondria fatty acids in the form of acyl-CoA molecules are progressively cleaved by β-oxidation to generate ATP. The process is initiated at the carboxyl end and involves the successive disruption of the link between the α-2 and β-3 carbon atoms (Lavoie and Gauthier 2006). At the end of each cycle the chain is reduced by two carbon atoms, and one molecule of FADH2, NADH and acetyl CoA is produced. The acetyl-CoA is then further oxidised within the mitochondria via the citric acid cycle, while the FADH2 and NADH enter the electron-transport chain. The process is repeated until the whole chain is oxidised.

Microsomal (α and ω) oxidation occurs within the endoplasmic reticulum by members of the cytochrome P450 family. They catalyse the oxidation of a variety of exogenous and endogenous compounds and play a relatively minor role in fatty acid oxidation.

2.3.11.2. VLDL SYNTHESIS

The addition of a single glycerol molecule to three fatty acids forms a triglyceride. Triglycerides cannot freely cross hepatocyte membranes, and so are either stored within the hepatocyte itself, or are coated in lipoproteins, incorporated within VLDL, and exported into the systemic circulation. VLDLs are formed within the liver and are a complex fusion of lipoproteins (predominantly 21

Apolipoprotein B-100), lipids and phospholipids. VLDL secretion facilitates the transfer of intra-hepatic fatty acids to peripheral adipose stores (Gibbons, Wiggins et al. 2004).

2.3.11.3. STORAGE WITHIN THE HEPATOCYTES

The final option for fatty acids is of conversion to triglycerides and storage within the hepatic cytosol. Factors that directly promote hepatic triglyceride storage are poorly understood.

Intra-hepatic storage appears to occur when fatty acid production exceeds the liver's oxidation or exportation abilities.

Apoprotein C II and insulin are activators of this enzyme and apoprotein C III is an inhibitor. After lipolysis is complete, a chylomicron remnant is released back into the circulation and is cleared rapidly by the liver, by a specific receptor mediated interaction which involves recognition of apoprotein E. The major component of the newly secreted chylomicrons are apoproteins B 48 and AI. In the lymphatics, the chylomicrons acquire apoproteins C and E mainly from HDL particles. VLDL is synthesized endogenously by the liver. The core lipid is triglyceride, and 20 % is cholesterol.

The major apoprotein is apoprotein B 100. But apoprotein C and E are also present. Normally after overnight fast, chylomicrons are cleared from the plasma and triglyceride circulates as VLDL. The metabolsim of VLDL is similar to chylomicrons, VLDL transports triglycerides to tissues to be used as fuel, or to the adipose tissue for storage. After interaction with lipoprotein lipase, a VLDL remnant is produced which is converted to LDL or removed by the liver via a specific receptor interaction involving apoprotein E.

HDL is important for removal of cholesterol from the peripheral tissues to the liver and for metabolism of chylomicrons and VLDL. The liver and intestine secrete nascent HDL particles, which take up cholesterol from chylomicrons and VLDL to become HDL3.

After esterification of plasma HDL cholesterol by enzyme LCAT lecithin cholesterol acyl transferase, further uptake of cholesterol transforms HDL3 to HDL2. HDL2 can transfer cholesterol to VLDL to be taken up by the liver, or deliver cholesterol directly to liver after conversion to HDL3 by hepatic triglyceride lipase.

2.3.11.4. LIPID TRANSPORT

2.3.11.4.1. THE EXOGENOUS PATHWAY

The dietary triglycerides and cholesterol are incorporated into large lipoprotein complexes called chylomicrons within the intestinal epithelial cells. The chylomicrons are secreted into the intestinal lymph and pass into general circulation for transport to the capillaries of adipose tissue and skeletal muscle where they adhere to the binding sites on capillary walls, while bound to these endothelial surfaces the chylomicrons are exposed to the enzyme lipoprotein lipase. Also the chylomicrons contain an apoprotein, apoprotein C-11 activates lipase liberating free fatty acids (FFA) and monoglycerides.

Through the endothelial cells there fatty acids enter the underlying adipocytes or muscle cells, where they are either reesterified to triglycerides or oxidized (27 & 29). The rest of the chylomicron dissociates from the capillary endothelium and reenters the circulation.

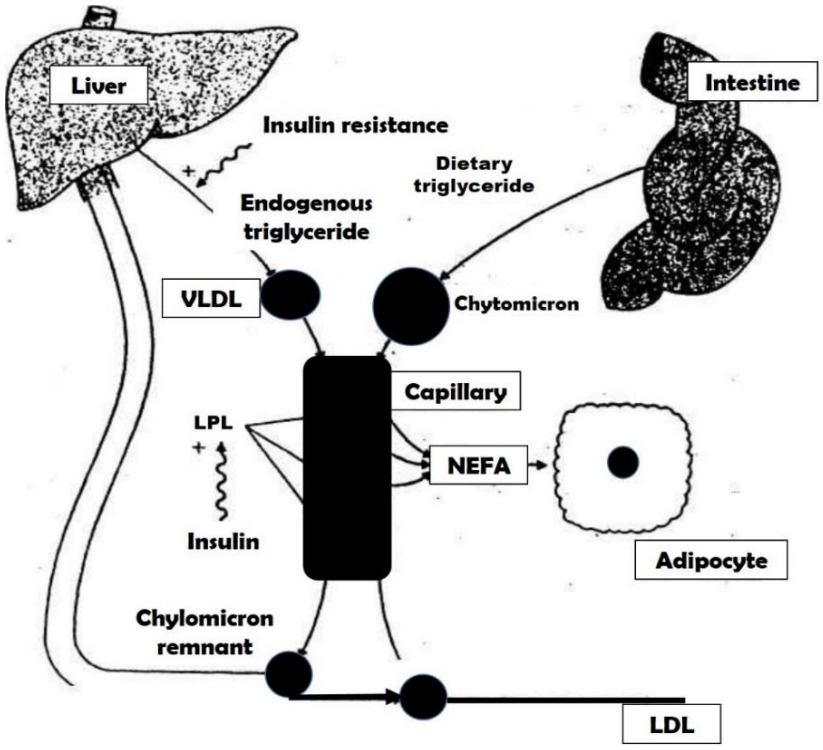


Fig.19. Mechanisms of VLDL

It will now form a compound relatively poor in triglycerides and enriched in cholesteryl esters. Ultimately chylomicron is converted into a chylomicron remnant particle which is transported and taken up by the liver, this is mediated by binding of apoprotein E to specific receptors called chylomicron remnant receptors. The surface bound remnant particles are taken into the cell and degraded. The overall result of chylomicron process is to delivery dietary triglycerides to adipose tissue and cholesterol to the liver. In the liver some of cholesterol gets converted to bile acids, which are excreted into the intestine to acts as detergents and facilitates absorption of dietary fat.

2.3.11.4.2. THE ENDOGENOUS PATHWAY

Carbohydrates gets converted to fatty acids in the liver, it also esterifies the fatty acids with glycerol to form glycerides and most endogenous cholesterols produced in the liver. From the liver VLDL particles are transported to tissue capillaries. In peripheral tissues they are removed in the same way as chylomicrons (Hydrolysis by the Enzyme Lipoprotein Lipase).

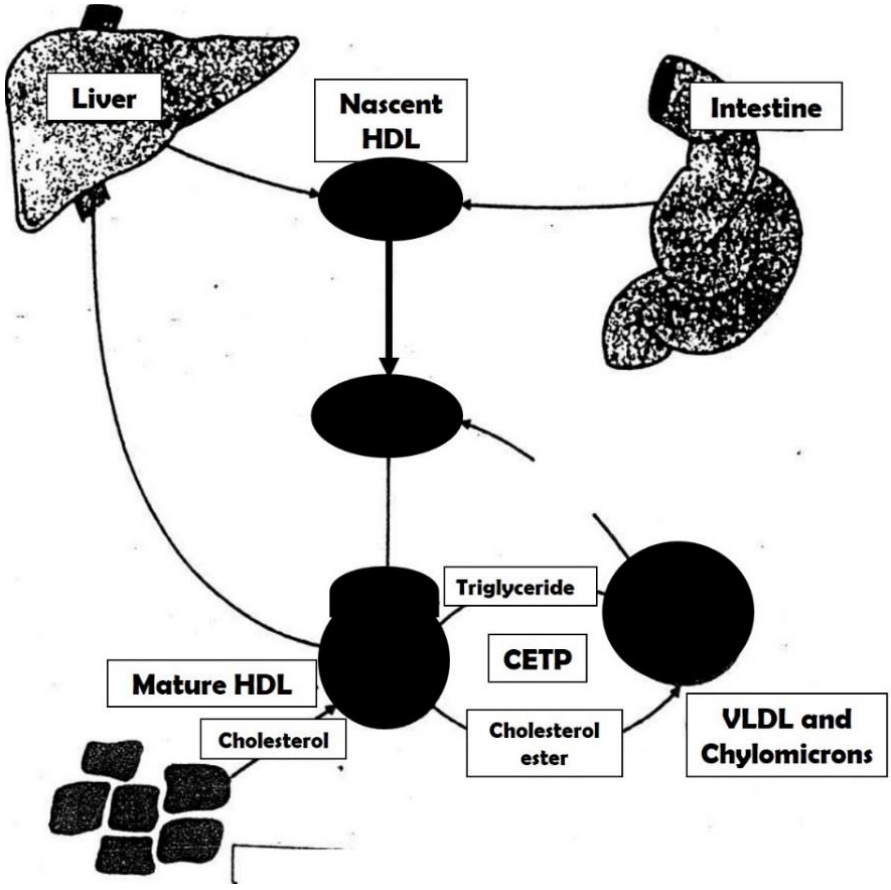


Fig.20. Mechanisms of HDL

The remnants generated from the action of lipoprotein lipase on VLDL are designated as intermediate density lipoprotein. Through LDL receptors a portion of LDL particle is catabolized by the liver the remaining LDL remain in plasma. Ultimately transformation of LDL particle to cholesterol rich LDL (28 & 29).

The function of LDL is to supply cholesterol to a variety of extra hepatic parenchymal cells such as adrenal cortical cells, lymphocytes, muscles cells and renal cells. These cells have LDL receptors localized on the cell surface. The molecule is bound and enters the cells where the cholesterol is used, released and become available to the cell for membrane synthesis (29).

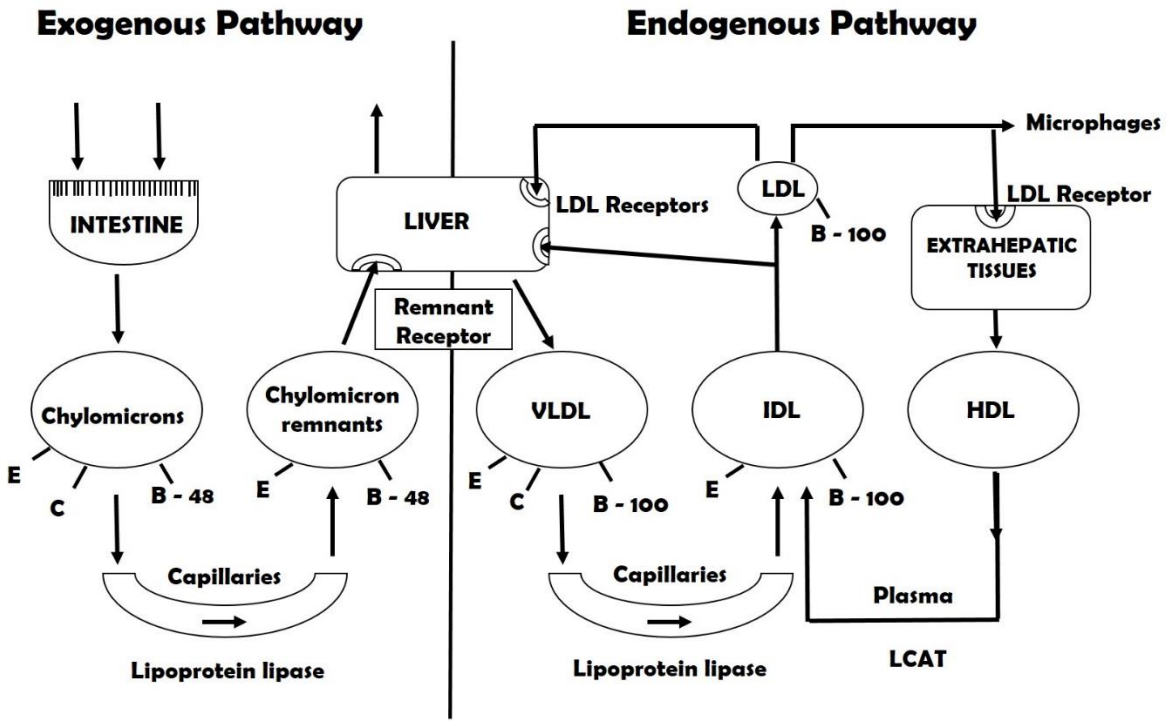


Fig.21. Lipoprotein Metabolism

This bindings and uptake of LDL suppresses endogenous synthesis. When the membranes of parenchymal and Scavenger cells undergo turnover and the cells die and removed, unesterified cholesterol is released into plasma where it binds, initially to HDL (catalyze by the plasma enzyme LCAT), transferred to VLDL and eventually appear in LDL.

This establishes a cycle by which LDL delivers cholesterol to extra hepatic cells and by which cholesterol is returned to LDL from extrahepatic cells via HDL. Most of the cholesterol released from extrahepatic tissue is transported to the liver for excretion in the bile.

The liver plays an essential role in lipid metabolism, several stages of lipid synthesis and transportation (32, 33 & 34). Alcohol consumption cause fatty liver, alcoholic hepatitis and ultimately, alcoholic cirrhosis in some patients (35, 36 & 37).

The liver plays a key role in the metabolism of plasma lipids and lipoproteins (38). Most of the endogenous cholesterol is synthesized in the hepatic microsomes, synthesis and metabolism of cholesterol is impaired in chronic liver disease resulting in a decrease in plasma levels (39).

Severe metabolic impairment in cirrhosis can produce a worsening of the serum lipoprotein pattern. High‐density lipoprotein (HDL) cholesterol and its major apolipoproteins have been shown to be reduced in cirrhosis, as also the serum levels of low‐density lipoprotein (LDL) cholesterol (39).

III. MATERIALS AND METHODS

3.1. STUDY DESIGN

This study is a single center non randomized prospective study meant to study lipid profile changes in patients with cirrhosis of liver.

3.2. STUDY PERIOD

Consecutive patients of cirrhosis admitted in Thanjavur medical college hospital during the period of January 2014 to august 2014 were taken up for the study.

3.3. STUDY CENTRE

This study was carried out in department of medicine Thanjavur medical college hospital, Thanjavur, Tamil nadu India. All cases were admitted and examine in details in the ward & clinical data was recorded in the profoma annexed herein.

3.4. CLINICAL DETAILS

Personal particular like age, sex details were obtained. Extensive history will be taken to rule out various other conditions which can lead to decrease in lipid

profile. Detailed past history were elicited and evidence of hepatic enchalopathy, hepatorenal syndrome and other major complication were notedand previous hospitalization were noted.

3.5. INCLUSION CRITERIA

- Age more than 18 years
- Known and established cases of Cirrhosis of liver by ultrasound abdomen and biochemical studies.

3.6. EXCLUSION CRITERIA

- Patients who had used Insulin or other Oral Hypoglycaemic drugs within previous 30 days.
- Patients who had used cholesterol lowering drugs within previous 30 days.
- Patients with other disease likely to decrease the lipid levels like Diabetes Mellitus, Hypertension, chronic smokers were excluded.

3.7. CLINICAL EXAMINATION

Clinical examination was done in a detailed manner and vital signs were recorded and systemic examination was carried out acites, slenomegaly and all other important were noted and recorded.

3.8. LIST OF INVESTIGATIONS DONE

- Total Leukocyte Count
- Differential Leukocyte Count
- Hemoglobin
- ESR
- Fasting Lipid Profile (Total cholesterol, Triglycerides, HDL, LDL)
- Random Blood Sugar
- Blood Urea
- Serum Creatinine
- LFT
- PT
- INR
- UGI scopy
- USG abdomen

3.9. LIPID PROFILE

Blood sample was collected in all patients who was in fasting state.

DATA AND STATISTICAL ANALYSIS (ANOVA)

The patient data was collected prospectively and entered into the profoma (Annexure) the data was digitalized in Microsoft excel software and statistical analysis it was done SPSS 20 software. The categorical variable have been described as proportion and percentage. The continuous variable have been expressed as mean and standard Deviation as well as range.

The effect of various future on lipid profile changes was analyzed by unpaired T- test (Difference between mean) for complications. Chi squire test have been used to compare the categorical data P-value < 0.05 was considered significant in the study.

IV. RESULTS AND ANALYSIS

This study was conducted 50 consecutive patients, with cirrhosis of liver got admitted in Thanjavur medical college Hospital studied over a period of eight month from January 2014 to Augusts 2014. This study to determine the levels of Total cholesterol, HDL, LDL and Triglycerides in cirrhotic patients. Extensive history was taken to rule out various other conditions which can lead to decrease in lipid profile.

Blood routine investigations such as hemoglobin, total leukocyte count, differential leukocyte count, ESR, Random blood sugar, Lipid profile and renal function tests LFT, PT, INR and UGI scopy will be done in order to rule out various other conditions which can lead to alter the lipid profile. The Lipid profile of patients LFT, PT, INR and UGI scopy and clinical complication were computed and analyzed.

4.1. AGE DISTRIBUTION

In our study of 50 patients below 40 were 32% of the total and above 40 years of age were 68 %. Among this 68 % maximum were in age group of 41 to 50 years of age which is 36% of total study group.

4.2. SEX AND ALCOHOLISM DISTRIBUTION

All the patients enrolled in our study were males. Among them 94 % were alcoholics. 6% were nonalcoholic.

4.3. LIPID PROFILE IN CIRRHOTIC PATIENTS IN GENERAL

- Among total of 50 patients of the patients 46% had total cholesterol below 140 and 54% of the patients had total cholesterol above 140.
- Among total of 50 patients 70 patients had HDL below 40 and 30% of the patients had above 40.
- Among total of 50 patients, 48%of the patients had LDL below 80 and 52% of the patients had above 80.
- Among total of 50 patients, 64% patients had below 150 and 36% of the patients had above 150.

4.4. CIRRHOTIC PATIENTS WITH ACSITIES OR SPLENOMEGALY

- Among total of 50 patients, 82 % patients were with ascites and 18 % without ascites.
- Among total of 50 patients, 88% patients were with splenomegaly and 12 % without splenomegaly.

4.5. LIPID PROFILE VARIATION IN CIRRHOTIC PATIENTS WITH VARIOUS PRESENTATIONS.

- LIPID PROFILE IN PATIENTS WITH HISTORY OF HEPATIC ENCEPHALOPATHY (Previously Treated and Recovered)

The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie. Patients with history of encephalopathy (44%) and those without encephalopathy (54%) were not statistically significant with P value > 0.05.

- LIPID PROFILE IN PATIENTS WITH HISTORY OF HEPATO RENAL SYNDROME

The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with history of hepatorenal syndrome (36% of the total) and those without hepatorenal syndrome (64%) were statistically significant with P value < 0.05.

- LIPID PROFILE IN PATIENTS WITH LOW AND NORMAL SERUM ALBUMIN

The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with low serum albumin (72%) and those with normal serum albumin (28%) were statistically significant with P value < 0.05.

- LIPID PROFILE IN PATIENTS WITH VARICES AND WITHOUT VARICES IN UGI SCOPY.

The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with varices (68%) and those without varices (32%) were not statistically significant with P value > 0.05.

In our study of 50 patients patients below 40 were 32% of the total and above 40 years of age were 68 %. Among this 68 % maximum were in age group of 41 to 50 years of age which is 36% of total study group.

Table. 2: AGE DISTRIBUTION

Particulars	No. of respondents (n=50)	Percentage (100%)
Below 40yrs	16	32.0
41 to 50yrs	18	36.0
51 to 60yrs	12	24.0
61yrs & above	4	8.0

Fig. 22: AGE DISTRIBUTION

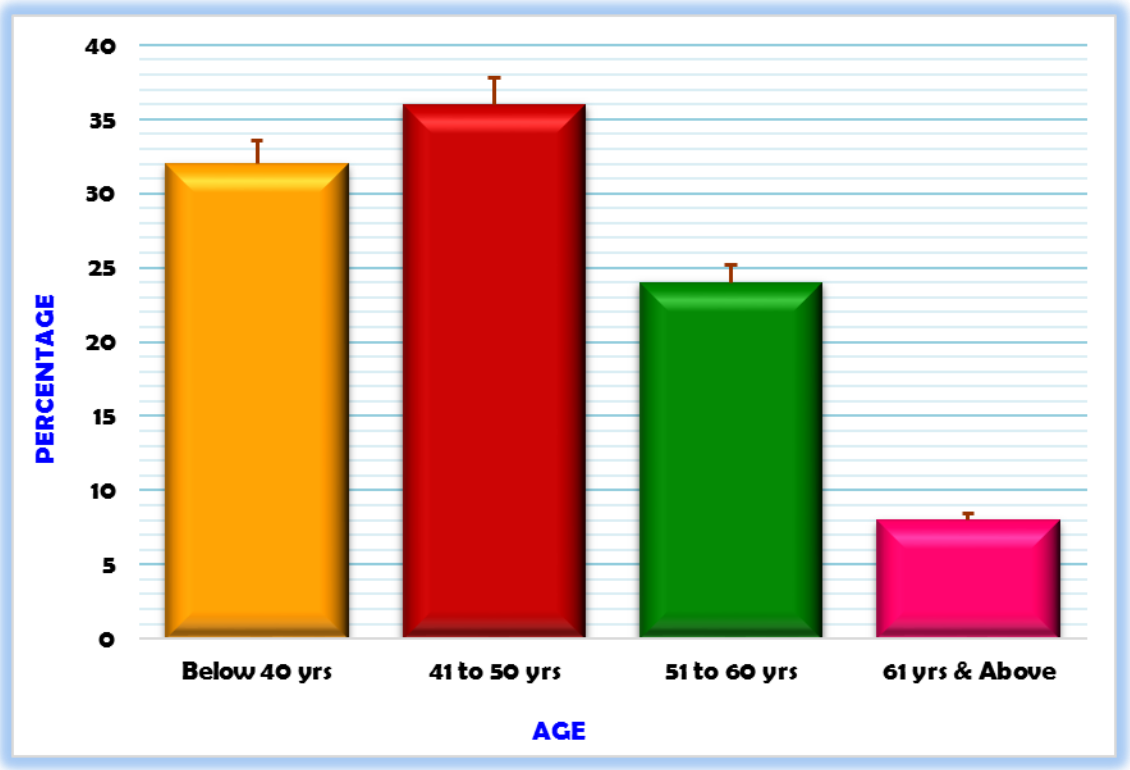
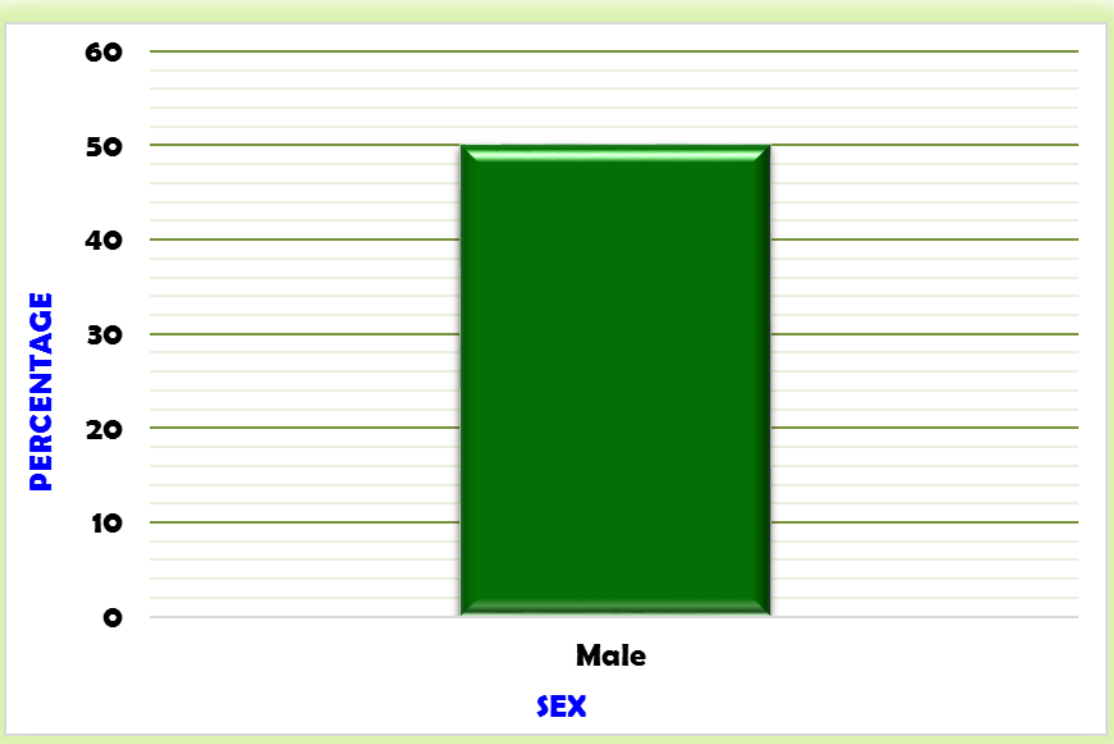


Table. 3: SEX DISTRIBUTION

Particulars	No. of respondents (n=50)	Percentage (100%)
Male	50	100.0

Fig. 23: SEX DISTRIBUTION



All the patients enrolled in our study were males. Among them 94 % were alcoholics. 6% were nonalcoholic.

Table. 4: ALCOHOLISM DISTRIBUTION

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	3	6.0
Positive	47	94.0

Fig. 24: ALCOHOLISM DISTRIBUTION

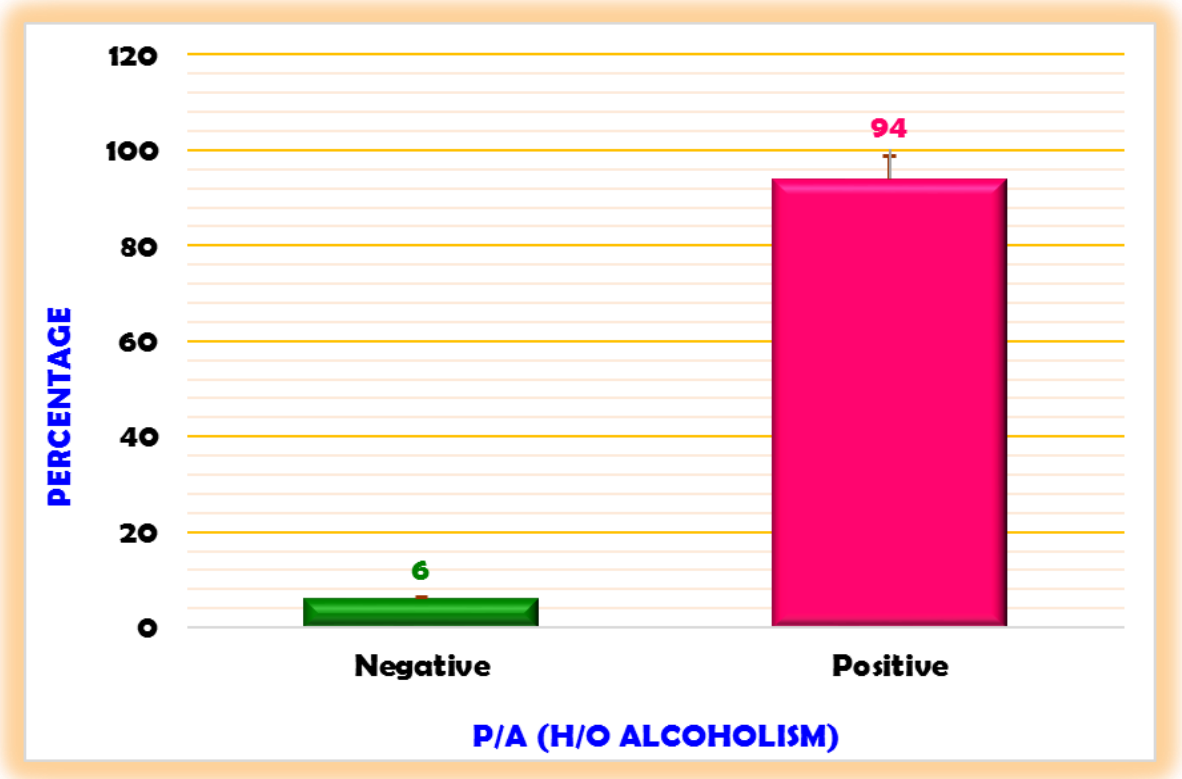
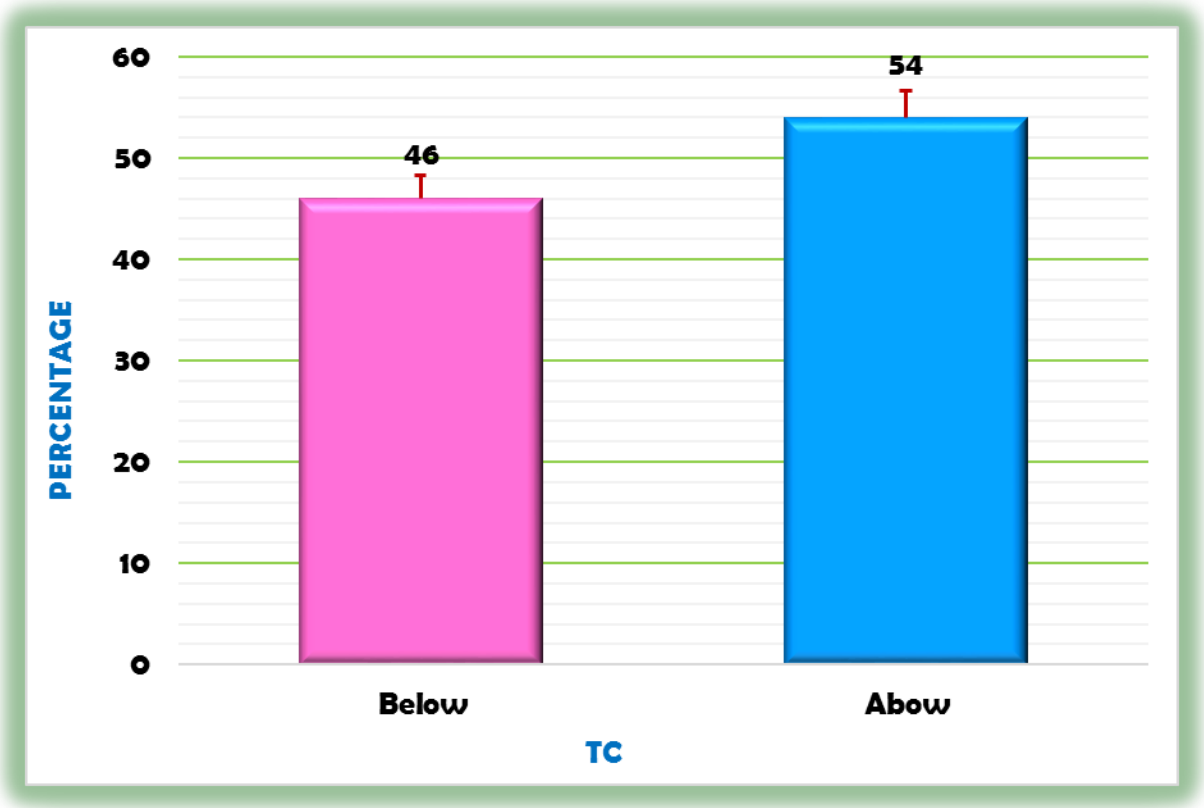


Table. 5: DISTRIBUTION OF TOTAL CHOLESTEROL

PARTICULARS	NO.OF RESPONDENTS (N=50)	PERCENTAGE (100%)
Below 140	23	46.0
Above 140	27	54.0

Fig. 25: DISTRIBUTION OF TOTAL CHOLESTEROL

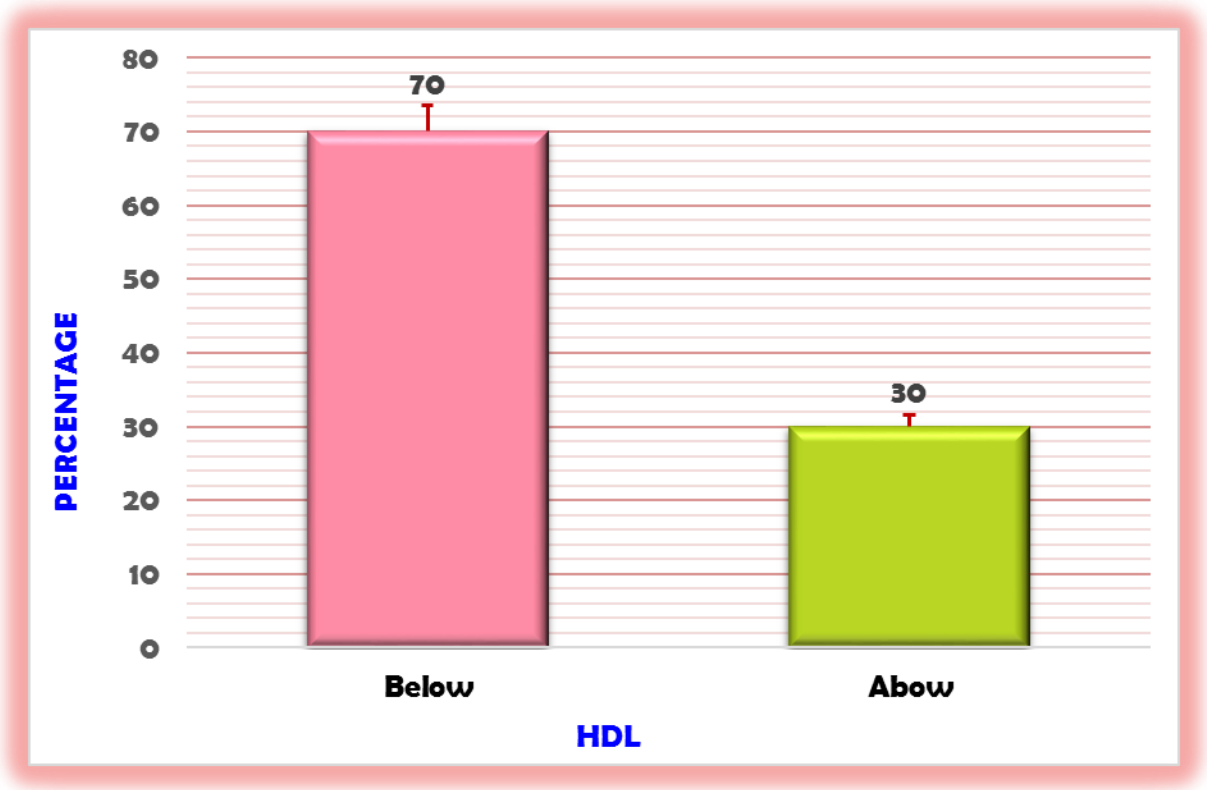


Among total of 50 patients of the patients 46% had total cholesterol below 140 and 54% of the patients had total cholesterol above 140.

Table. 6: DISTRIBUTION OF HIGH DENSITY LIPOPROTEIN

PARTICULARS	NO.OF RESPONDENTS (N=50)	PERCENTAGE (100%)
Below 40	35	70.0
Above 40	15	30.0

Fig. 26: DISTRIBUTION OF HIGH DENSITY LIPOPROTEIN



Among total of 50 patients 70 patients had HDL below 40 and 30% of the patients had above 40.

Table. 7: DISTRIBUTION OF LOW DENSITY LIPOPROTEIN

PARTICULARS	NO.OF RESPONDENTS (N=50)	PERCENTAGE (100%)
Below 80	24	48.0
Above 80	26	52.0

Fig. 27: DISTRIBUTION OF LOW DENSITY LIPOPROTEIN

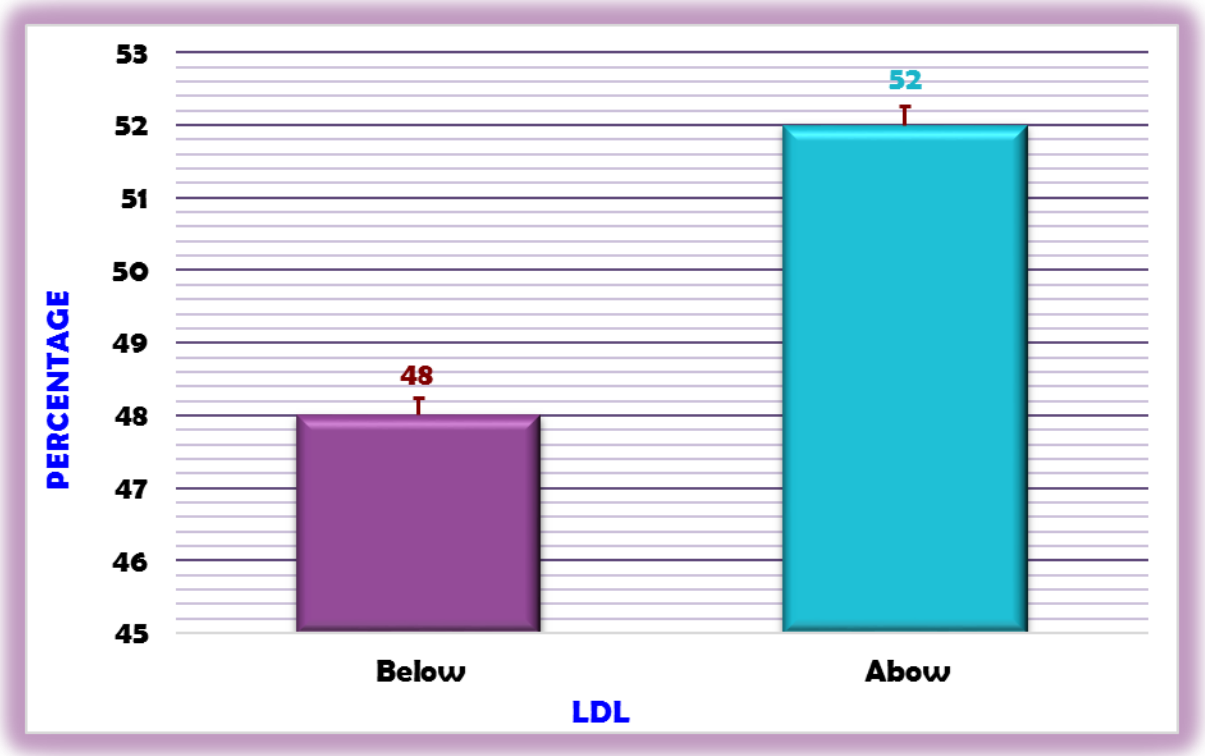
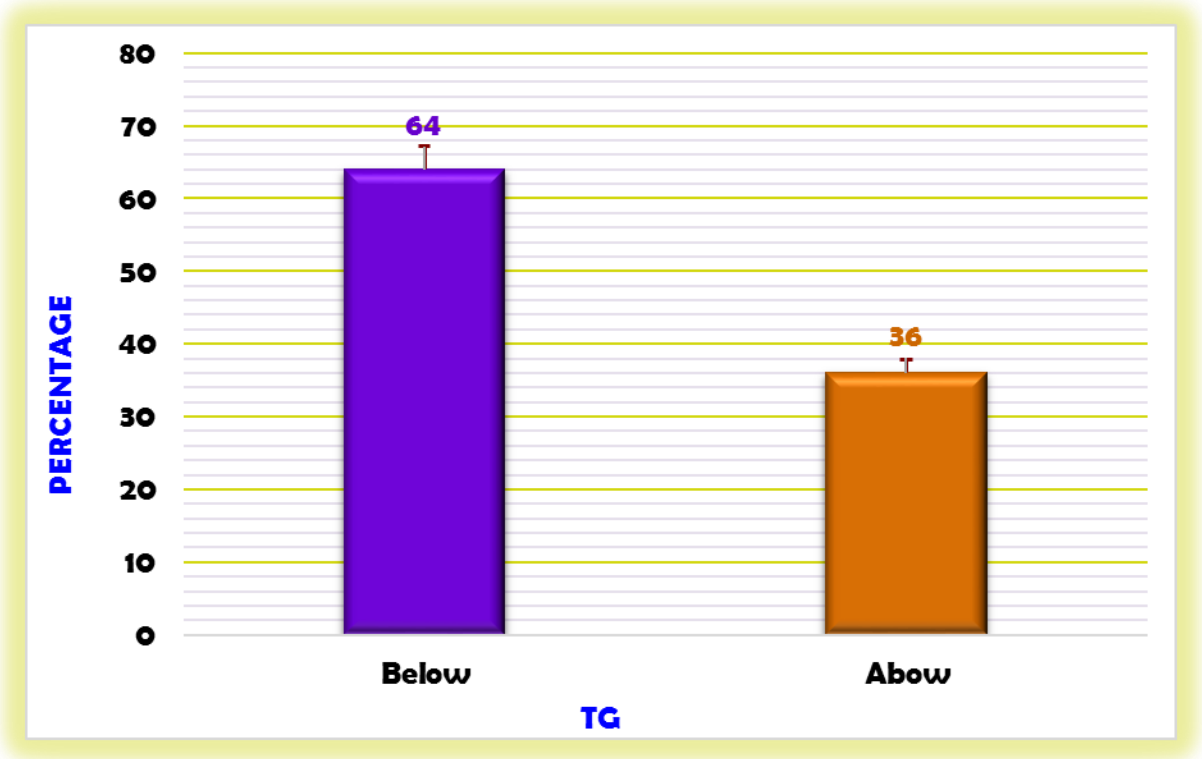


Table. 8: DISTRIBUTION OF TRIGLYCERIDE

PARTICULARS	NO.OF RESPONDENTS (N=50)	PERCENTAGE (100%)
Below 150	32	64.0
Above 150	18	36.0

Fig. 28: DISTRIBUTION OF TRIGLYCERIDE



Among total of 50 patients, 64% patients had below 150 and 36% of the patients had above 150.

Table. 9: DISTRIBUTION OF COMPLICATION

PARTICULARS	NO.OF RESPONDENTS (N=50)	PERCENTAGE (100%)
Normal	2	4
Complicate	48	96.0

Fig. 29: DISTRIBUTION OF COMPLICATION

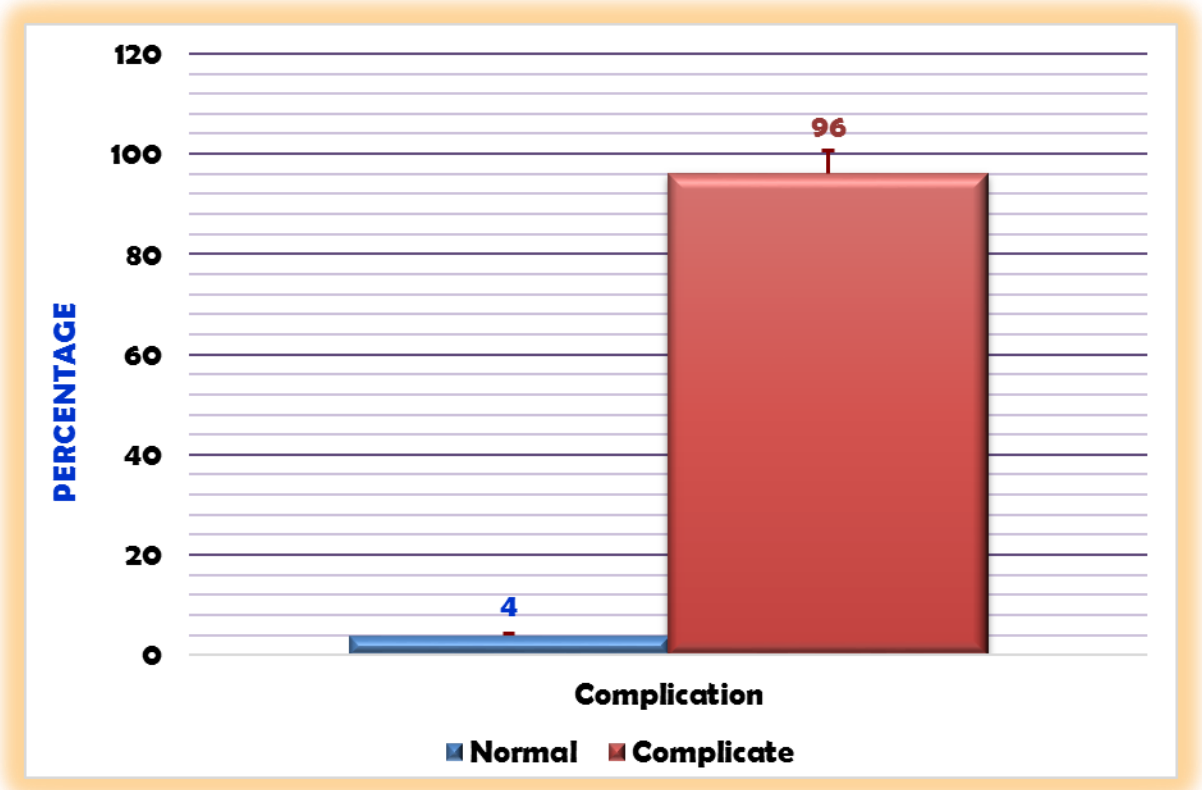


Table. 10: COMPLICATION CORRELATED TO LIPIDS DISTRIBUTION

PARTICULARS	Complication						STATISTICAL INFERENCE
	Normal		Complicate		Total		
	(n=2)	(100%)	(n=48)	(100%)	(n=50)	(100%)	
TC Below 140	1	50%	22	45.8%	23	46.0%	X^2=0.13 Df=1.908>0.05 Not Significant
Above 140)	1	50%	26	54.2%	27	54.0%	
HDL Below 40	2	100%	33	68.8%	35	70.0%	X^2=.893 Df=1.345>0.05 Not Significant
Above 40	0	0%	15	31.3%	1524	30.0%	
LDL Below 80	1	50%	23	47.9%	26	48.0%	X^2=.003 Df=1.954>0.05 Not Significant
Above 80	1	50%	25	52.1%	32	52.0%	
TG Below 150	1	50%	31	64.6%	18	64.0%	X^2=.177 Df=1.674>0.05 Not Significant
Above 150	1	50%	17	35.4%	36	36.0%	

Fig. 30: COMPLICATION CORRELATED TO LIPIDS DISTRIBUTION

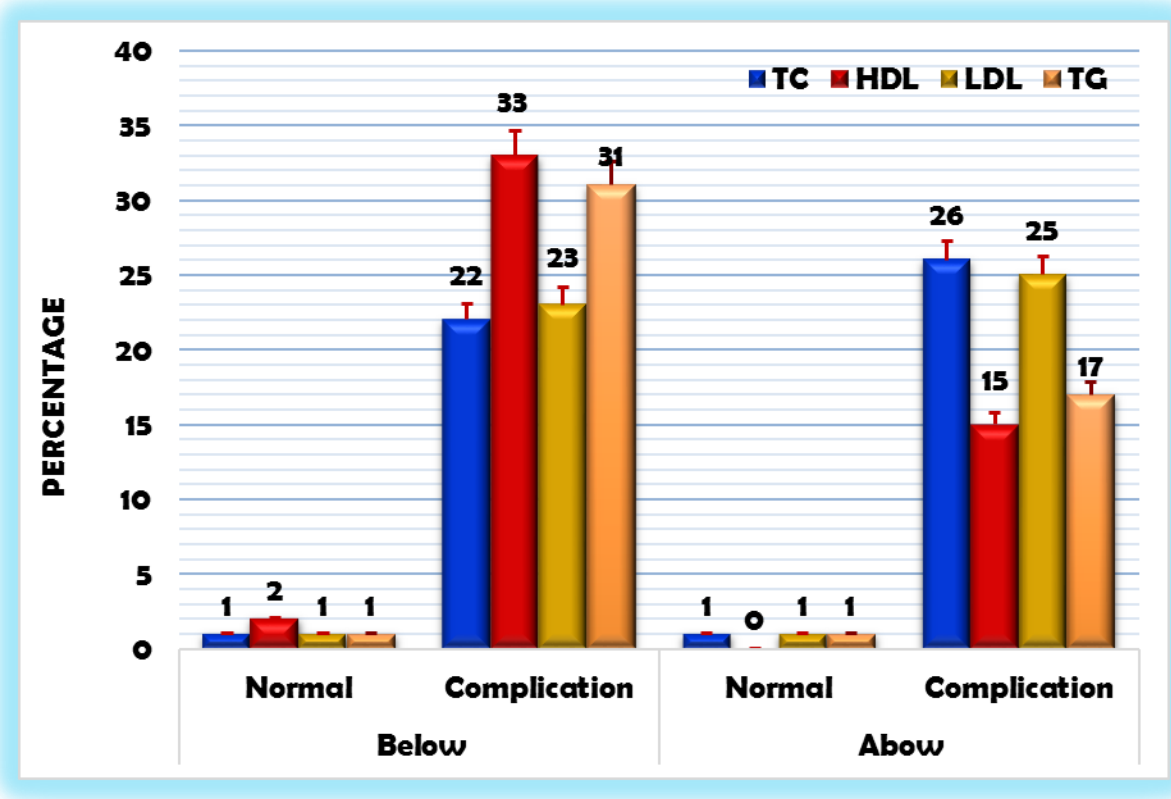


Table. 11: EVIDENCE OF HEPATIC ENECEPHALOTHY

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	28	56.0
Positive	22	44.0

Fig. 31: EVIDENCE OF HEPATIC ENECEPHALOTHY

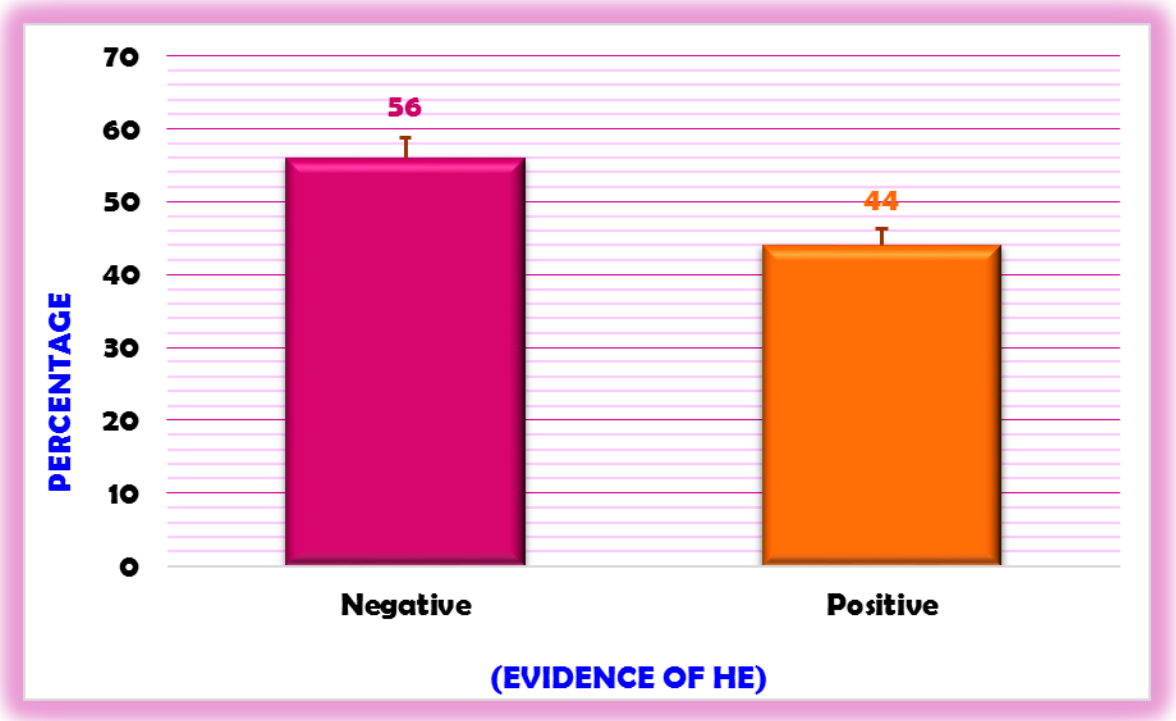


Table. 12: EVIDENCE OF HEPATO RENAL SYNDROME

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	32	64.0
Positive	18	36.0

Fig. 32: EVIDENCE OF HEPATO RENAL SYNDROME

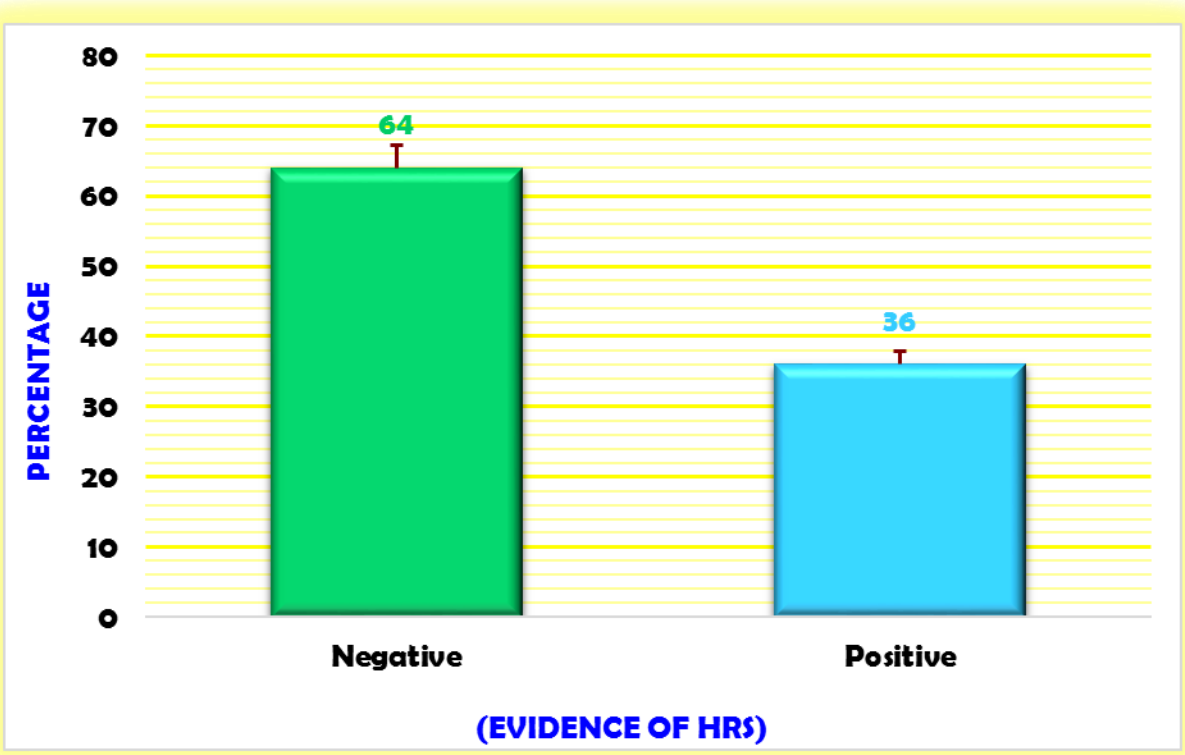
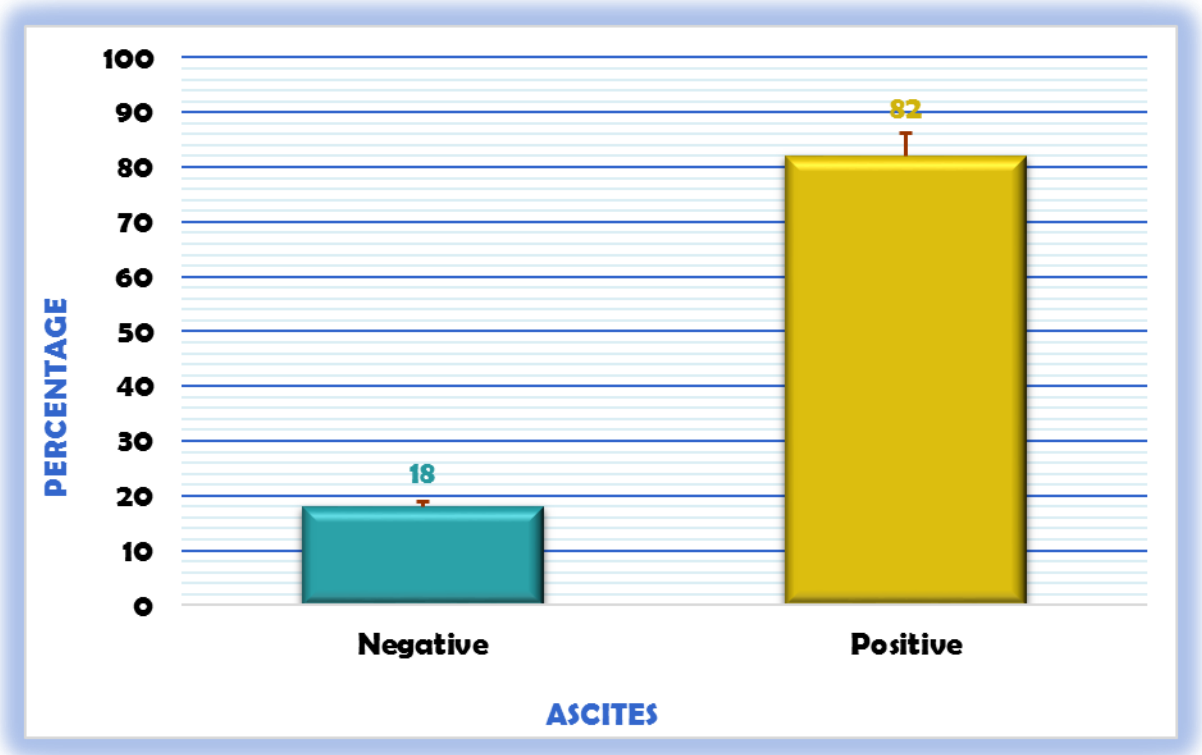


Table. 13: FEATURES OF ASCITES

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	9	18.0
Positive	41	82.0

Fig. 33: FEATURES OF ASCITES

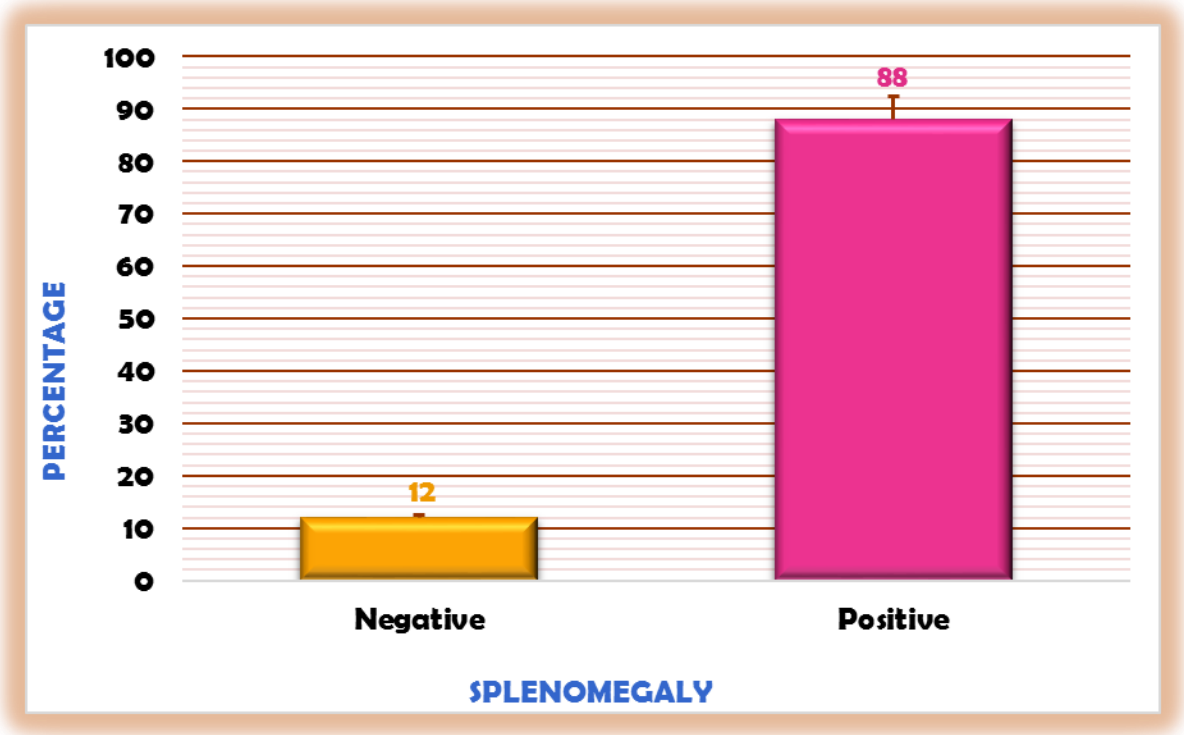


Among total of 50 patients, 82 % patients were with ascites and 18 % without ascites.

Table. 14: EVIDENCE OF SPLENOMEGALY

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	6	12.0
Positive	44	88.0

Fig. 34: EVIDENCE OF SPLENOMEGALY



Among total of 50 patients, 88% patients were with splenomegaly and 12 % without splenomegaly.

Table. 15: DISTRIBUTION OF SERUM ALBUMINE

Particulars	No. of respondents (n=50)	Percentage (100%)
Below 3	36	72.0
Above 3	14	28.0

Fig. 35: DISTRIBUTION OF SERUM ALBUMINE

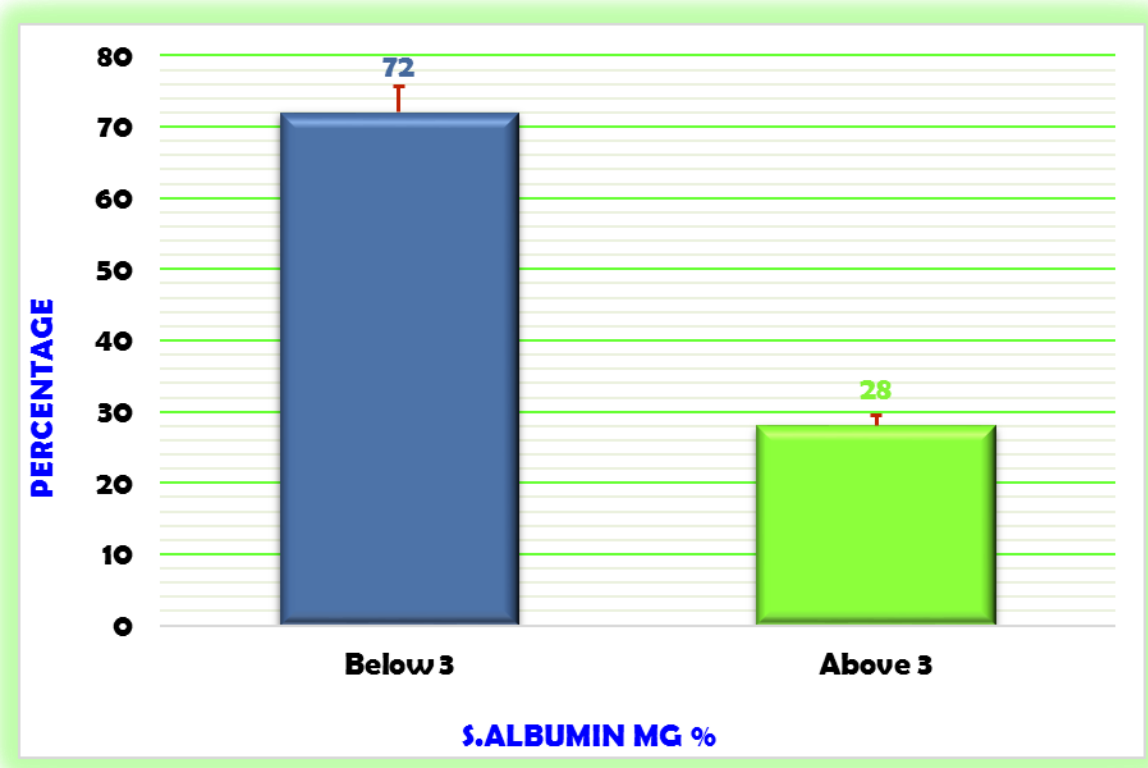


Table. 16: EVIDENCE OF VARIES IN UGI SCOPY

Particulars	No. of respondents (n=50)	Percentage (100%)
Negative	16	32.0
Positive	34	68.0

Fig. 36: EVIDENCE OF VARIES IN UGI SCOPY

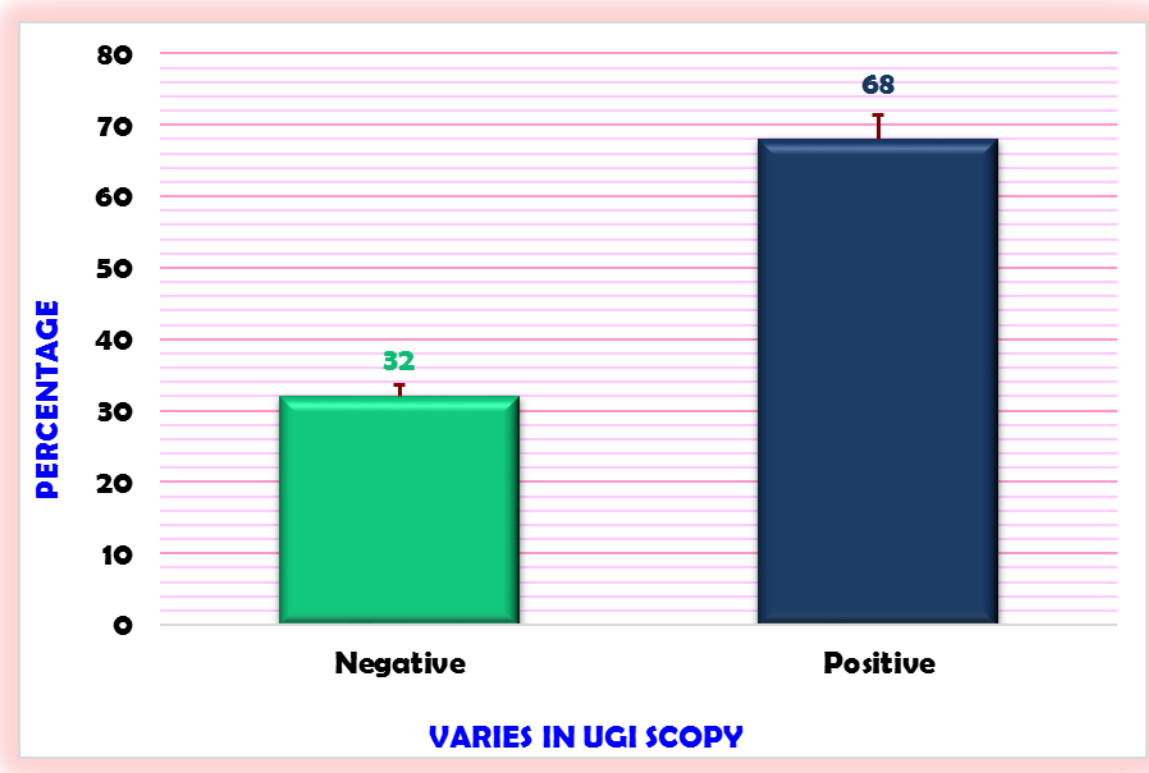


Table. 17: DISTRIBUTION OF LIPIDS

Item	Minimum	Maximum	Means	S.D
Age	28	65	46.68	9.728
Duration	0	35	18.18	8.376
TC	90	206	146.22	36.933
HDL	25	50	38.10	5.891
LDL	45	134	80.12	25.712
TG	60	230	133.06	44.545
VLDL	12	46	26.96	8.762
S.ALBUMIN mg%	1.80	3.80	2.7680	.52506

Fig. 37: DISTRIBUTION OF LIPIDS

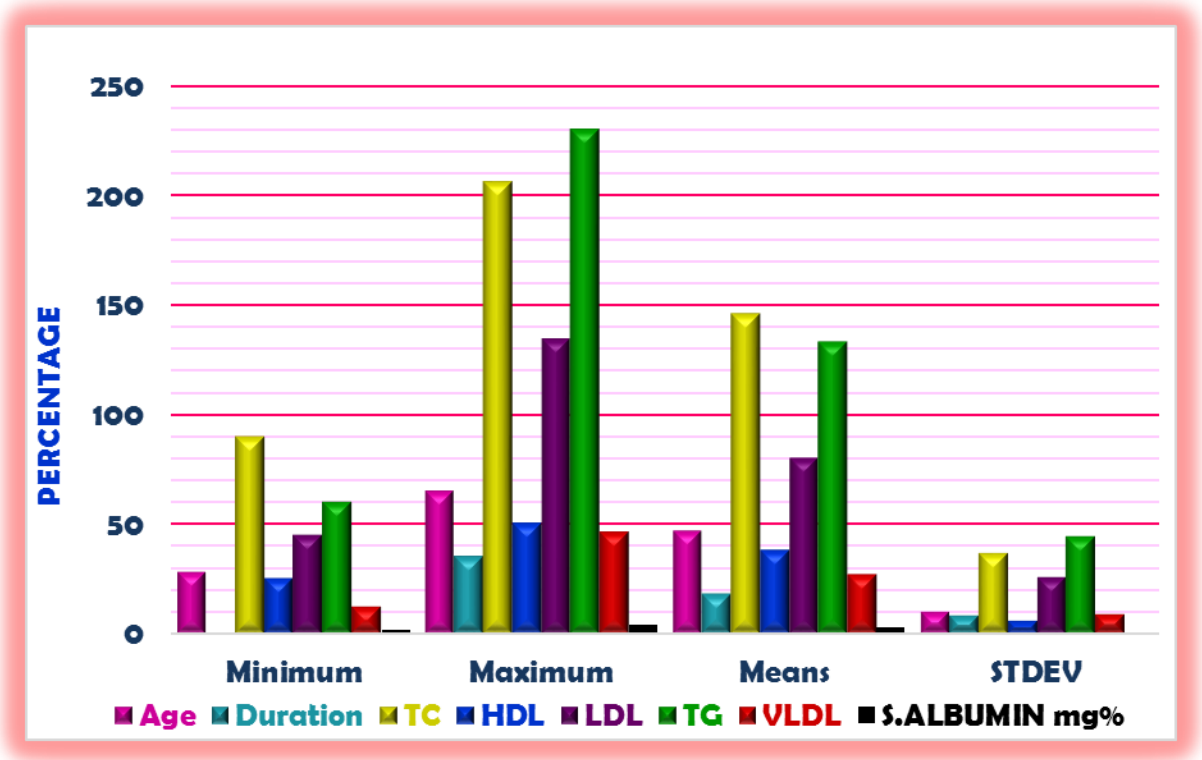


Table. 18: HRS LIPIDS CORELATION

(EVIDENCE OF HE)	MEAN	S.D	STATISTICAL INFERENCE
TC	148.96	33.951	T=.589 Df=48
Negative (n=28)			.559>0.05
Positive (n=22)	142.73	40.962	Not Significant
HDL	38.86	5.414	T=1.026 Df=48
Negative (n=28)			.310>0.05
Positive (n=22)	37.14	6.446	Not Significant
LDL	83.39	22.125	T=1.016 Df=48
Negative (n=28)			.315>0.05
Positive (n=22)	75.95	29.678	Not Significant
TG	132.25	43.420	T=-.144 Df=48
Negative (n=28)			.886>0.05
Positive (n=22)	134.09	46.946	Not Significant

Fig. 38: HRS LIPIDS CORELATION

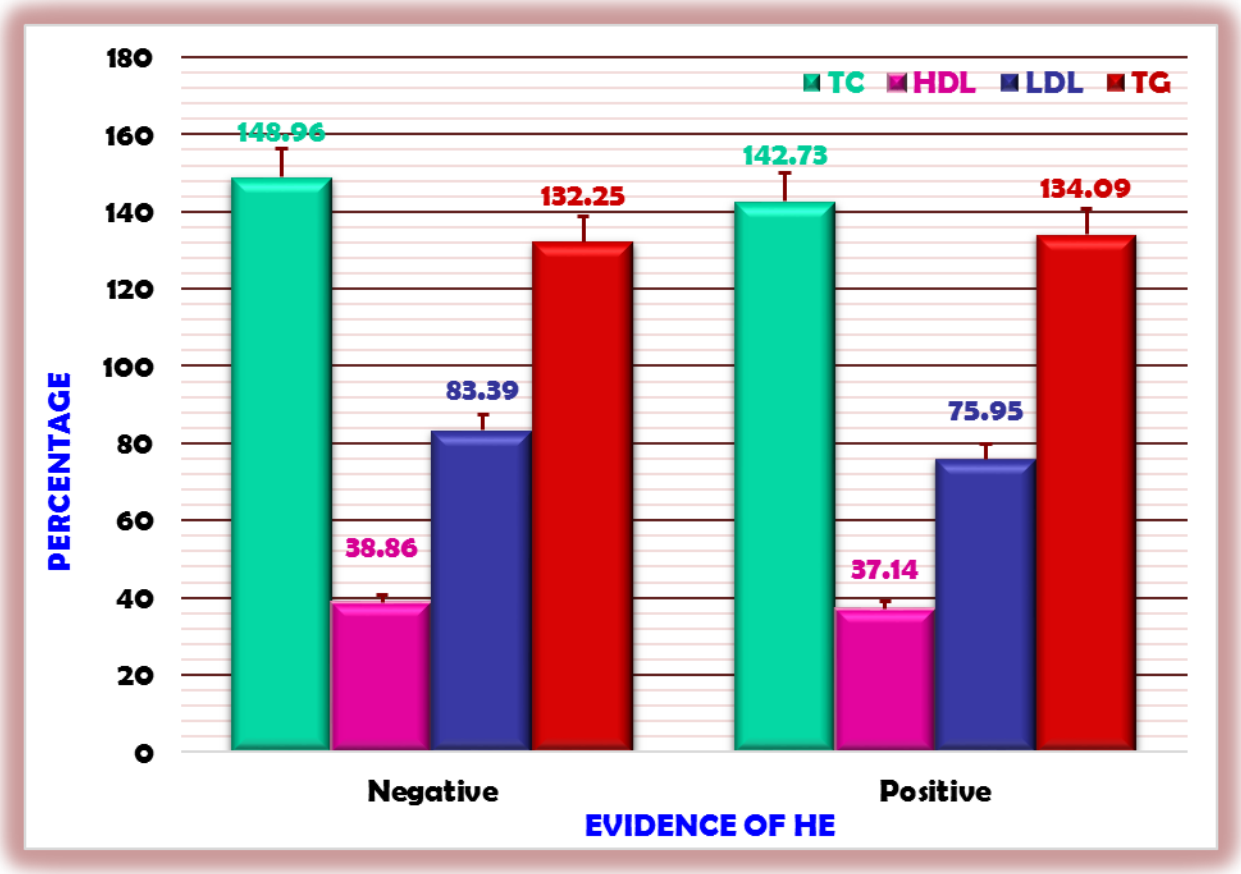
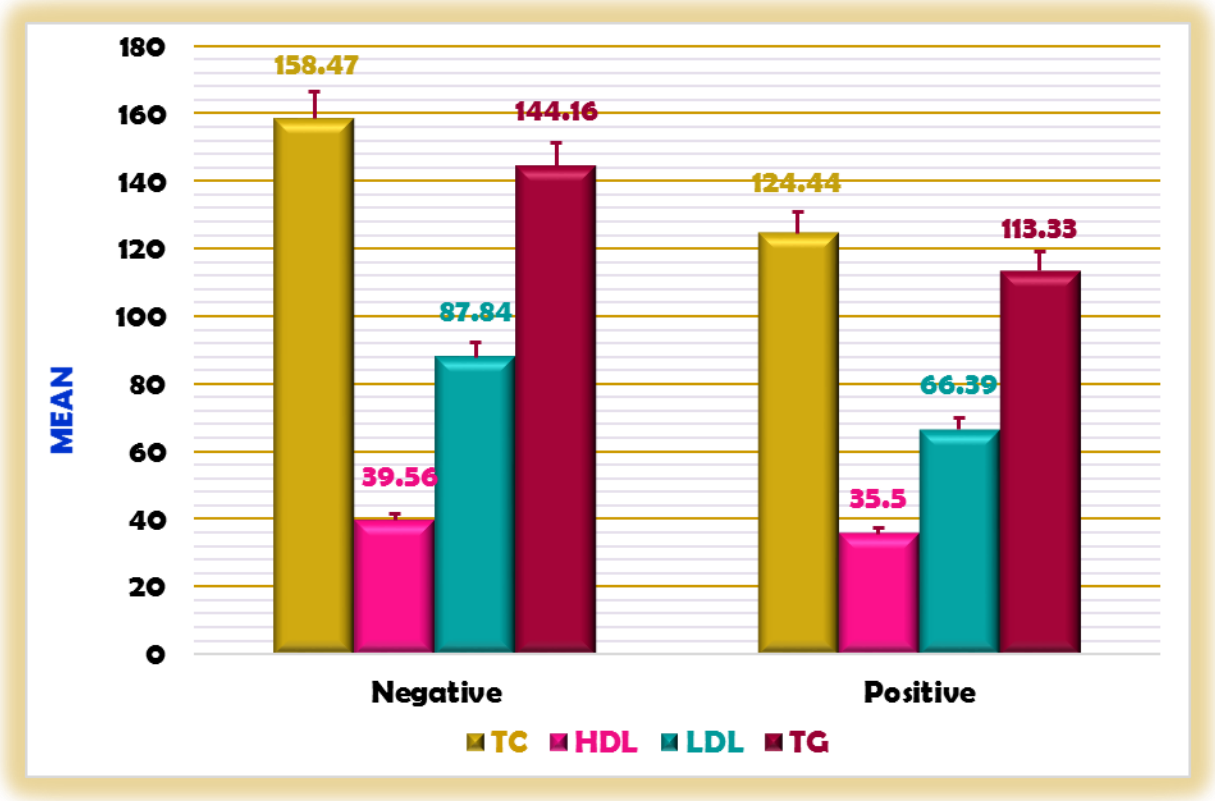


Table. 19: LIPIDS DISTRIBUTION IN HRS

HRS (EVIDENCE OF)	MEAN	S.D	STATISTICAL INFERENCE
TC Negative (n=32)	158.47	31.735	T=3.459 Df=48 .001<0.05 Significant
Positive (n=18)	124.44	36.204	
HDL Negative (n=32)	39.56	5.376	T=2.458 Df=48 .018<0.05 Significant
Positive (n=18)	35.50	6.012	
LDL Negative (n=32)	87.84	22.750	T=3.065 Df=48 .004<0.05 Significant
Positive (n=18)	66.39	25.493	
TG Negative (n=32)	144.16	42.949	T=2.468 Df=48 .017<0.05 Significant
Positive (n=18)	113.33	41.373	

Fig. 39: LIPIDS DISTRIBUTION IN HRS

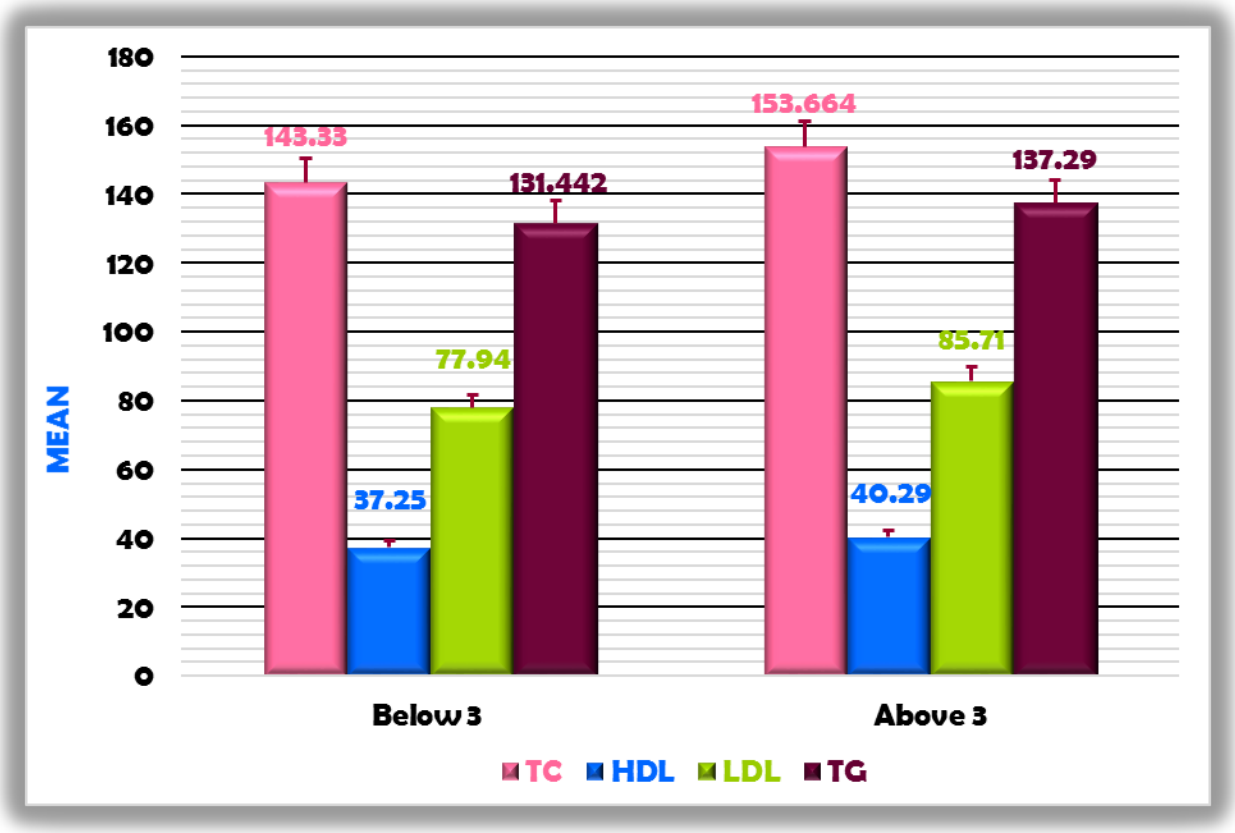


The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with history of hepatorenal syndrome (36% of the total) and those without hepatorenal syndrome (64%) were statistically significant with P value < 0.05.

Table. 20: SERUM ALBUMINE IN LIPIDS DISTRIBUTION

S.ALBUMIN mg%	MEAN	S.D	STATISTICAL INFERENCE
TC	143.33	38.417	T=-.884 Df=48
Below 3 (n=36)			.381>0.05
Above 3 (n=14)	153.64	32.947	Not Significant
HDL	37.25	6.044	T=-1.665 Df=48
Below 3 (n=36)			.102>0.05
Above 3 (n=14)	40.29	5.030	Not Significant
LDL	77.94	26.441	T=-.959 Df=48
Below 3 (n=36)			.343>0.05
Above 3 (n=14)	85.71	23.724	Not Significant
TG	131.42	45.881	T=-.415 Df=48
Below 3 (n=36)			.680>0.05
Above 3 (n=14)	137.29	42.245	Not Significant

Fig. 40: SERUM ALBUMINE IN LIPIDS DISTRIBUTION

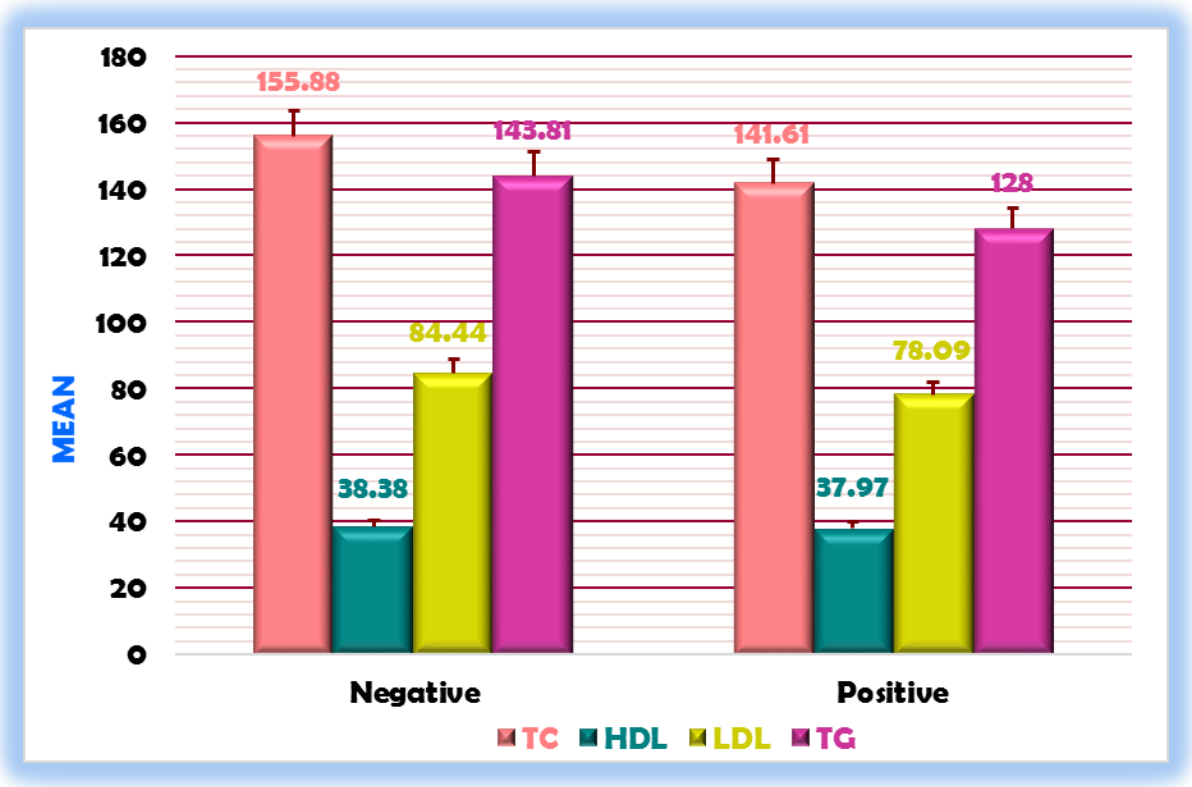


The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with low serum albumin (72%) and those with normal serum albumin (28%) were statistically not significant with P value > 0.05.

Table. 21: VARIES IN UGI SCOPY OF DISTRIBUTION

VARIES IN UGI SCOPY	MEAN	S.D	STATISTICAL INFERENCE
TC			
Negative (n=16)	155.88	39.804	T=1.276 Df=48
Positive (n=34)	141.68	35.196	.208>0.05 Not Significant
HDL			
Negative (n=16)	38.38	6.076	T=.224 Df=48
Positive (n=34)	37.97	5.890	.824>0.05 Not Significant
LDL			
Negative (n=16)	84.44	30.774	T=.812 Df=48
Positive (n=34)	78.09	23.193	.421>0.05 Not Significant
TG			
Negative (n=16)	143.81	45.496	T=1.175 Df=48
Positive (n=34)	128.00	43.852	.246>0.05 Not Significant

Fig. 41: VARIES IN UGI SCOPY OF DISTRIBUTION



The difference in mean of total cholesterol, HDL, LDL. TG among two groups ie patients with varices (68%) and those without varices (32%) were not statistically significant with P value > 0.05.

DISCUSSION

Lipids are the important components of cellular function and also homeostasis. Liver play a very essential role in lipid metabolism and various stages of lipid synthesis and transportation. Therefore we expect an abnormal lipid profile in those with cirrhosis. There is reduced level of serum cholesterol triglyceride, high density lipoprotein and low density lipoprotein in patient with chronic liver dysfunction because of reduction of lipoprotein biosynthesis (45).

In our study 50 cirrhotic patient included among this 36% were 41 to 50 years of age group others are evenly distributed. In Nigerian medical journal shows the same result and international monthly journal in the field of hepatology also the same result that alcoholic cirrhosis is involved 41 to 50 years of age.

In our study group 94% of population gave the history of alcohol consumption. Nigerian medical journal January February 2013 shows the similar results in that all cases were male, except one. They observed that majority of the cases (51%) had consumed alcohol regularly for a period of 5‑10 years, followed by 22% cases having consumed alcohol for 10‑15 years (41).

We noted that total cholesterol below the normal level in 46% of the patients included in our study group. High density lipoprotein were low in 70% of the study group, low density lipoprotein was low in 48% and 64% have low triglyceride level in our study group.

Various study gave the similar result in Nigerian medical journal January February 2013 shows the median total cholesterol and HDL cholesterol were significantly low compared with controls groups and LDL cholesterol low level but statistically not significant.

The international monthly journal in the field of hepatology December 2010 shows there was a significant decrease in serum triglyceride, total, HDL and LDL cholesterol levels also the low level in patient with cirrhosis is inversely related with the severity of the cirrhosis (40).

Journal of the Arab society for medical research 2012 the triglyceride, total, HDL and LDL cholesterol is impaired in cirrhotic patient irrespective of the incidence of hepatocellular carcinoma in those patients.

The total and LDL cholesterol, triglyceride level was inversely related to the severity of cirrhosis without HCC. In cirrhosis associated with hepato cellular carcinoma HDL cholesterol have an inverse correlation to the severity of the disease.

In our study population 50 patients with cirrhosis 48 patients have various complications like acites, splenomagly, hapatic in encephalopathy, hepato renal syndrome varices about 98% of the total populations.

We stratified the data with respect to Total cholesterol, Triglycerides, HDL, LDL although we stood the statistical analysis to find that whether theirs any significant correlation between the lipids abnormality and complication of cirrhosis.

It failed to show any significant association with lipids profile abnormality with various complication of cirrhosis of liver.

Though our study report shows that cirrhosis is associated with low cholesterol levels, we proceeded to correlate the two major complications including Hepatorenal syndrome and hepatic encephalopathy. HRS is found to have statistically significant correlation with the low lipid levels. But there was no association with hepatic encephalopathy.

Investigation like serum albumin and varices in UGI scopy result were found to be not statistically significant.

However the result of the study serve as a baseline for further study in lipid profile changes in cirrhosis. Further study in this field warranted. In future it may provide valid relation between cirrhosis severity and lipid profile changes.

CONCLUSION

This study was carried out in 50 patients of cirrhosis and we arrived at the following conclusions.

- 46% of patients shows significant reduction in total cholesterol.
- Among them 70% of them had High Density Lipoproteins cholesterol reduction.
- The Low Density Lipoproteins was reduced in 48% of the study population.
- Triglyceride also shows the similar trend in reduction almost 64 % had the low level.
- Various complication of cirrhosis failed to shows any significant association with low lipid profile but the hepato renal syndrome shows the significant correlation with the low lipids level.
- In our study there is no correlation between the severity of the cirrhosis of liver and low lipids profile changes abnormality.
- So lipid profile should be used as a routine screening test in cirrhosis.
- These values help to ascertain the prognosis and severity.

BIBLIOGRAPHY

1. S. R. Abdel-Misih and M. Bloomston, "Liver anatomy," Surgical Clinics of North America, vol. 90, no. 4, p. 643, 2010.
2. W. W. Lautt, "Mechanism and role of intrinsic regulation of hepatic arterial blood flow: hepatic arterial buffer response," American Journal of Physiology-Gastrointestinal and Liver Physiology, vol. 249, no. 5, pp. G549–G556, 1985.
3 O. Ohtani and Y. Ohtani, "Lymph circulation in the liver," The Anatomical Record, vol. 91, no. 6, pp. 643–652, 2008.
4. F. Kiernan, "The anatomy and physiology of the liver," Philosophical transactions of the Royal Society of London, vol. 123, pp. 711–770, 1833.
5. J. S. Dooley, A. Lok, A. Burroughs, and J. Heathcote, Sherlock's diseases of the liver and biliary system, 12th ed. Wiley-Blackwell, 2011.
6. A. Rappaport, Z. Borowy, W. Lougheed, and W. Lotto, "Subdivision of hexagonal liver lobules into a structural and functional unit. Role in hepatic physiology and pathology," The Anatomical Record, vol. 119, no. 1, pp. 11–33, 1954.
7. R. Taub, "Liver regeneration: from myth to mechanism," Nature Reviews Molecular Cell Biology, vol. 5, no. 10, pp. 836–847, 2004.

8. B. C. Isenberg and J. Y. Wong, “Building structure into engineered tissues,” Materials Today, vol. 9, no. 12, pp. 54–60, 2006.

9. P. Anthony, K. Ishak, N. Nayak, H. Poulsen, P. Scheuer, and L. Sobin, “The Morphology of cirrhosis. Recommendations on definition, nomenclature, and Classification by a working group sponsored by the world health organization.” Journal of clinical pathology, vol. 31, no. 5, pp. 395–414, 1978.

10. F. H. Netter, The netter collection of medical illustrations. Digestive System: Liver, Biliary tract, Pancreas. Saunders, 1964, vol. 3.

11. D. Schuppan and N. H. Afdhal, “Liver cirrhosis,” The Lancet, vol. 371, no. 9615, pp. 838–851, 2008.

12. M. Iannacone, G. Sitia, Z. M. Ruggeri, and L. G. Guidotti, “Hbv pathogenesis in animal models: recent advances on the role of platelets,” Journal of hepatology, vol. 46, no. 4, pp. 719–726, 2007.

13. A. Gramenzi, F. Caputo, M. Biselli, F. Kuria, E. Loggi, P. Andreone, and M. Bernardi, “Review article: alcoholic liver disease–pathophysiological aspects and risk factors,” Alimentary pharmacology & therapeutics, vol. 24, no. 8, pp. 1151–1161, 2006.

14. R. D. Odze and J. R. Goldblum, Surgical Pathology of the GI Tract, Liver, Biliary Tract, and Pancreas, 2nd ed. Saunders, 2009.

15. S. L. Friedman, “Mechanisms of hepatic fibrogenesis,” Gastroenterology, vol. 134, no. 6, pp. 1655–1669, 2008.

16. C. Kordes, I. Sawitza, A. Müller-Marbach, N. Ale-Agha, V. Keitel, H. Klonowski-Stumpe, and D. Häussinger, “Cd133+ hepatic stellate cells are progenitor cells,” Biochemical and biophysical research communications, vol. 352, no. 2, pp. 410–417, 2007.

17. R. F. Hanna, D. A. Aguirre, N. Kased, S. C. Emery, M. R. Peterson, and C. B. Sirlin, “Cirrhosisassociated hepatocellular nodules: Correlation of histopathologic and mr imaging features1,” adiographics, vol. 28, no. 3, pp. 747–769, 2008.

18. P. Huet, C. Goresky, J. Villeneuve, D. Marleau, and J. Lough, “Assessment of liver microcirculation in human cirrhosis.” Journal of Clinical Investigation, vol. 70, no. 6, p. 1234, 1982.

19. J. Villeneuve, M. Dagenais, P. Huet, A. Roy, R. Lapointe, and D. Marleau, “The hepatic microcirculation in the isolated perfused human liver,” Hepatology, vol. 23, no. 1, pp. 24–31, 1996.

20. E. Vanheule, A. M. Geerts, J. Van Huysse, D. Schelfhout, M. Praet, H. Van Vlierberghe, M. De Vos, and I. Colle, “An intravital microscopic study of the

hepatic microcirculation in cirrhotic mice models: relationship between fibrosis and angiogenesis," International journal of experimental pathology, vol. 89, no. 6, pp. 419–432, 2008.

21. H. Hano and S. Takasaki, "Three-dimensional observations on the alterations of lobular architecture in chronic hepatitis with special reference to its angioarchitecture for a better understanding of the formal pathogenesis of liver cirrhosis," Virchows Archiv, vol. 443, no. 5, pp. 655–663, 2003.
22. Y. Fukukura, O. Nakashima, A. Kusaba, M. Kage, and M. Kojiro, "Angioarchitecture and blood circulation in focal nodular hyperplasia of the liver," Journal of hepatology, vol. 29, no. 3, pp. 470–475, 1998.
23. V. Gülberg, K. Haag, M. Rössle, and A. L. Gerbes, "Hepatic arterial buffer response in patients with advanced cirrhosis," Hepatology, vol. 35, no. 3, pp. 630–634, 2002.
24. G. Garcia-Tsao, S. Friedman, J. Iredale, and M. Pinzani, "Now there are many (stages) where before there was one: in search of a pathophysiological classification of cirrhosis," Hepatology, vol. 51, no. 4, pp. 1445–1449, 2010.
25. G. Garcia-Tsao, R. J. Groszmann, R. L. Fisher, H. O. Conn, C. E. Atterbury, and M. Glickman, "Portal pressure, presence of gastroesophageal varices and variceal bleeding," Hepatology, vol. 5, no. 3, pp. 419–424, 1985.

26. W. K. Al-Hamoudi, "Cardiovascular changes in cirrhosis: Pathogenesis and clinical implications," Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association, vol. 16, no. 3, p. 145, 2010.

27. Daniel J.Rader,Helen H, Hobbs *et al.*,Disorders of lipoprotein metabolism, In Fauci,Braundald,Kasper *et al.*,Harrison'sprinciples of internal medicine,17th edi,Newyork,USA,2008:P2416. 34)

28. Durrington PN. Lipid and lipoprotein disorders. Chapter 11.6 In Weatherall DJ, Ledingham G and Warrel DA Edt. Oxford Textbook of Medicine. 3rd edition, Vol. 2, New York, Oxford Medical Publications, 1996: p.1413.

29. Peter A Mayer *et al.*, Lipid Transport and storage, cholesterol synthesis, transport and excretion, In Robert K. Murray, Daryl K, Granner *et al.*,, Harper's Illustrated Biochemistry, 26th edition, 2003; 205: p 219.

30. Wade S, Smith, Sclaiborne Johnston *et al.*, Cerebrovascular diseases. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, Edt. Harrison's Principles of Internal Medicine, 16th edition, New York, USA, 2005; 2: pp. 2372.

31. Albucher JF, Ferrieros J *et al.*, Serum lipids in young patients with ischaemic stroke, a case control study. J Neurology Neurosurgery Psychiatry 2000; 69 (1): 29-33.

32. McIntyre N. Plasma lipids and lipoproteins in liver disease. Gut 1978; 19:526−530.

33. Kroon PA, Powell EE. Liver, lipoproteins and disease: I. Biochemistry of lipoprotein metabolism. J Gastroenterol Hepatol 1992; 7:214‑24.

34. Ghadir MR, Riahin AA, Havaspour A, Nooranipour M, Habibinejad AA. The Relationship between lipid profile and severity of liver damage in cirrhotic patients. Hepat Mon 2010; 10:285‑8.

35. Lelbach WK. Cirrhosis in the alcoholic and its relation to the volume of alcohol abuse. Ann N Y Acad Sci 1975; 252:85‑105.

36. Becker U, Deis A, Sorensen TI, Gronbaek M, Borch‑Johnsen K, Muller CF, *et al.*, Prediction of risk of liver disease by alcohol intake, sex, and age: A Prospective population study. Hepatology 1996; 23:1025‑9.

37. Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapeutic targets. Gastroenterology 2011; 141:1572‑85.

38. Canbay A, Bechmann L, Gerken G. Lipid metabolism in the liver. Z Gasteroenterol 2007; 45:35‑41.

39. Jarike AE, Momoh JA. Plasma total cholesterol, high density lipoprotein cholesterol and low density lipoprotein cholesterol levels in liver cirrhosis in Nigerians. Nig Qt J Hosp Med 1996; 6:157‑9.

40. Mohammad reza ghadir *et al.,,* the relationship between lipid profile and severity of liver damage in cirrhotic patients. Hepat mon: 2011:10(4):285-288.

41. Phukan JP, Sinha A, Deka JP. Serum lipid profile in alcoholic cirrhosis: A study in a teaching hospital of north-eastern India. Niger Med J 2013; 54:5-9.

42. Gao B, Bataller R. Alcoholic liver disease: Pathogenesis and new therapeutic Targets. Gastroenterology 2011; 141:1572‑85.

43. Tome S, Lucey MR. Review article: Current management of alcoholic liver disease. Aliment Pharmacol Ther 2004; 19:707‑14.

44. Khairy H. *et al.,,* lipid profile among cirrhotic patients with and without hepatocellular carcinoma in Upper Egypt, The journal of arab society for medical research.2012:7:33-37

45. Halsted CH. Nutrition and alcoholic liver disease. Semin liver Dis. 2004; 24(3):289-304.

PROFORMA

Name :	IP No :
Age :	D.O.A :
Sex :	D.O.D :
Religion :	Hospital :
Address :	Occupation :

I. PRESENTING COMPLAINTS:

1. Distention of abdomen
2. Swelling of lower limbs
3. Pain abdomen
4. Mass per abdomen
5. Fever
6. Yellowish discoloration of eyes
7. Altered sensorium
8. Dyspeptic symptoms
9. Loss of apetite/weight
10. Haemetamesis
11. Bleeding per rectum
12. Sleep disturbance

II. PASTHISTORY

a. Similar ailments like presenting symptoms

b. Previous hospitalization for reduced output ,altered sensorium.

c. History of Jaundice

d. Blood transfusion

e. Intake of Hepatotoxic drugs

f. History of Immunization

g. Past history of any abdominal operations

h. Other illness

III. PERSONAL HISTORY

a. Diet : Veg./mixed

b. Sleep : Disturbed/undisturbed

c. Alcohol consumption : Duration

d. Bowel and micturition habits

Regular :

Constipation/Diarrhoea :

e. Apetitc :

IV. GENERAL PHYSICAL EXAMINATION

Built	:	Nourishment	:
Scalp hair	:	Weight	:
Skin	:	Height	:
Conjunctiva	:	Sclera	:

Oral cavity :

Neck : Lymph node enlargement : Yes / No

Thyroid enlargement : Yes / No

Parotid enlargement : Yes / No

Upper Limbs : Flapping tremors

Dupytrens contracture

Palmar erythema

Spider Navei

Oedema : Pitting/non pitting :

Jugular venous pulse :

Foetar hepaticus :

Anaemia :

Icterus :

Cyanosis :

Clubbing :

Lymph nodes :

Gynaecomastia :

Vital signs : Pulse/min :

Blood pressure in mm Hg :

Temperature :

Respiratory rate :

V. SYSTEMIC EXAMINATION:

I. *Abdominal Examination:*

a. Inspection

Shape : Scaphoid/uniform distention

Umbilicus : Transverse/vertical eversion

Skin over the abdomen : Dry/tense/glistening

Dilatation of abdominal wall veins: Around umbilicus/Flanks

Movements of all quadrants of abdomen : Normal/Restricted

Visible persistalisis :

Scars and sinuses :

Hernial orifices :

b. Palpation

Edema of the abdominal wall

Muscle guarding/rigidity

Tenderness

Abdominal girth at umbilical level

Liver : Palpable : Yes/No

Size : Cms below right costal margin in mid clavicular line

Consistency : Soft/firm/hard

Surface : Smooth/Nodu1ar/Irregu1ar

Border : Sharp/Blunt

Tenderness : Present/Absent

Spleen : Palpable : Yes/No

Size : Cms below left costal margin in mid clavicular Line

Consistency : Soft/firm/hard

Tenderness : Present/Absent

Any other palpable mass :

Measurements of abdomen:

Abdominal girth at umbilicus :

Distance between umbilicus and pubic symphysis :

Distance between umbilicus and xiphisternum :

c. Percussion

Fluid thrill : Present/Absent

Shifting dullness : Present/Absent

Liver dullness : cms below right costal margin mid clavicular line

Splenic dullness : Present/Absent

d. Ausculitatiion

Over Liver : Rub/Bruie

Over spleen : Rub

Bowel sounds :

e. External Genatalia :

2. Cardio Vascular system examination

3. *Respiratory system examination*

4. *Central nervous system examination*

IX. INVESTIGATIONS

1. Routine Haematological examination

Hb gm% :

Total Count :

Differential count :

2. Urine analysis : Sugar :

Albumin : Microscopy :

Bile salts/Bile pigments :

Urobilinogen :

3. Random blood sugar in mg/dl :

4. Blood urea in mg/dl :

5. Serum creatinine in mg/dl :

6. Liver function tests :

Serum total Billirubin :

Serum total proteins :

Serum Albumin :

Serum Globulin :

Albumin/Globulin ratio :

S.G.O.T :

S.G.P.T :

Serum Alkaline Phosphotase :

7. Lipid profile :

Tota cholesterol :

HDL :

LDL :

Triglyceride :

VLDL :

8.PT &INR :

8.ECG :

9.Ultrasound abdomen :

TREATMENT :

SUMMARY AND CONCLUSION :

MASTER CHART

S.No	IP NO.	AGE	SEX	H/O ALCOHOLISM		EVIDENCE OF		ASCITES	SPLENO MEGALY	TC	HDL	LDL	TG	VLDL	S.ALBUMIN mg%	VARIES IN UGI SCOPY
				P/A	DURATION IN YRS	HE	HRS									
1	4087	38	M	+	10	-	-	+	+	192	45	115	156	31	3.00	-
2	4075	46	M	+	20	+	-	+	+	167	39	47	105	21	2.80	-
3	4372	54	M	+	20	-	-	+	+	194	39	117	140	38	2.00	+
4	5692	56	M	+	25	+	+	+	+	170	40	92	190	38	3.50	+
5	12601	50	M	+	30	-	-	-	+	192	45	115	160	32	3.20	-
6	4396	28	M	+	10	-	+	+	+	146	37	90	95	19	3.00	+
7	7415	48	M	+	20	-	-	+	-	142	39	82	105	21	2.80	+
8	17404	48	M	+	25	+	-	+	+	196	39	118	195	39	2.40	-
9	13789	35	M	+	10	-	-	+	+	148	40	82	130	26	3.40	+
10	17984	35	M	+	10	+	+	+	+	138	36	79	75	23	2.20	+
11	18521	48	M	+	15	-	-	+	+	154	42	90	110	22	3.20	+
12	18138	56	M	+	20	-	-	-	-	206	40	120	230	46	3.00	-
13	28313	32	M	+	10	-	-	+	+	158	38	92	140	28	2.80	+
14	29375	45	M	+	15	-	-	+	+	156	40	91	125	25	3.20	+
15	38672	48	M	+	20	+	-	+	+	201	37	132	160	32	3.40	-

16	**4860**	**45**	**M**	**+**	**10**	**-**	**+**	**+**	**+**	**98**	**32**	**52**	**70**	**14**	**3.20**	**+**
17	**4329**	**32**	**M**	**+**	**12**	**+**	**+**	**+**	**+**	**204**	**42**	**134**	**190**	**38**	**3.00**	**+**
18	**23006**	**43**	**M**	**+**	**20**	**+**	**-**	**+**	**+**	**130**	**30**	**68**	**160**	**32**	**2.80**	**-**
19	**30085**	**58**	**M**	**+**	**25**	**-**	**-**	**+**	**+**	**194**	**44**	**108**	**220**	**42**	**2.60**	**+**
20	**38116**	**64**	**M**	**+**	**30**	**-**	**-**	**+**	**+**	**110**	**31**	**60**	**95**	**19**	**2.20**	**+**
21	**39314**	**65**	**M**	**+**	**25**	**+**	**+**	**+**	**+**	**104**	**36**	**50**	**90**	**18**	**2.00**	**-**
22	**34378**	**62**	**M**	**-**	**-**	**-**	**-**	**-**	**+**	**120**	**36**	**60**	**120**	**24**	**3.40**	**-**
23	**40213**	**31**	**M**	**+**	**20**	**-**	**+**	**+**	**+**	**114**	**40**	**52**	**110**	**22**	**3.00**	**+**
24	**41612**	**40**	**M**	**+**	**10**	**+**	**-**	**+**	**+**	**116**	**42**	**54**	**80**	**20**	**3.20**	**+**
25	**43702**	**40**	**M**	**+**	**10**	**-**	**-**	**+**	**+**	**126**	**34**	**70**	**110**	**22**	**3.00**	**+**
26	**37893**	**60**	**M**	**+**	**28**	**-**	**-**	**-**	**+**	**110**	**38**	**55**	**85**	**17**	**2.80**	**-**
27	**38012**	**55**	**M**	**+**	**30**	**+**	**+**	**+**	**+**	**124**	**37**	**50**	**135**	**27**	**2.20**	**-**
28	**38956**	**60**	**M**	**+**	**25**	**+**	**+**	**+**	**+**	**90**	**25**	**45**	**100**	**20**	**2.00**	**+**
29	**39103**	**35**	**M**	**+**	**20**	**+**	**+**	**+**	**+**	**93**	**29**	**48**	**80**	**16**	**1.80**	**+**
30	**39261**	**47**	**M**	**+**	**20**	**-**	**-**	**+**	**-**	**134**	**38**	**70**	**130**	**26**	**1.80**	**+**
31	**40374**	**38**	**M**	**+**	**20**	**-**	**-**	**-**	**-**	**137**	**35**	**75**	**135**	**27**	**2.80**	**+**
32	**2227**	**45**	**M**	**+**	**10**	**+**	**-**	**+**	**+**	**168**	**44**	**94**	**150**	**30**	**2.50**	**+**
33	**3769**	**50**	**M**	**+**	**20**	**-**	**-**	**+**	**-**	**172**	**45**	**90**	**185**	**37**	**3.20**	
34	**4544**	**41**	**M**	**+**	**15**	**-**	**+**	**+**	**+**	**164**	**46**	**86**	**160**	**32**	**2.60**	**+**

35	**14736**	**54**	**M**	**+**	**20**	**+**	**+**	**-**	**+**	**104**	**32**	**54**	**90**	**18**	**2.00**	**+**
36	**19428**	**52**	**M**	**-**	**-**	**-**	**-**	**-**	**+**	**186**	**45**	**102**	**192**	**38**	**3.50**	**+**
37	**25150**	**50**	**M**	**+**	**25**	**+**	**-**	**-**	**-**	**184**	**40**	**108**	**180**	**36**	**2.20**	**-**
38	**28901**	**55**	**M**	**+**	**30**	**+**	**+**	**+**		**98**	**30**	**52**	**80**	**16**	**2.90**	**+**
39	**29012**	**45**	**M**	**+**	**20**	**+**	**-**	**-**	**+**	**180**	**48**	**92**	**200**	**40**	**3.00**	**+**
40	**1692**	**38**	**M**	**+**	**10**	**-**	**-**	**+**	**+**	**146**	**37**	**90**	**95**	**19**	**3.40**	**+**
41	**1693**	**45**	**M**	**+**	**12**	**+**	**-**	**+**	**+**	**184**	**50**	**96**	**190**	**38**	**3.60**	**-**
42	**2921**	**38**	**M**	**+**	**18**	**-**	**-**	**+**	**+**	**174**	**44**	**98**	**160**	**32**	**2.60**	**-**
43	**9290**	**38**	**M**	**+**	**-**	**-**	**+**	**+**	**+**	**192**	**48**	**106**	**190**	**38**	**3.00**	**+**
44	**15080**	**60**	**M**	**+**	**28**	**+**	**+**	**+**	**+**	**90**	**35**	**45**	**100**	**20**	**2.00**	**+**
45	**16208**	**56**	**M**	**+**	**15**	**+**	**-**	**+**	**+**	**184**	**44**	**101**	**195**	**39**	**2.40**	**+**
46	**17493**	**32**	**M**	**+**	**18**	**-**	**-**	**+**	**+**	**102**	**25**	**65**	**60**	**12**	**2.80**	**-**
47	**80518**	**64**	**M**	**+**	**28**	**+**	**+**	**+**	**+**	**110**	**31**	**60**	**95**	**19**	**3.00**	**+**
48	**30911**	**40**	**M**	**+**	**30**	**-**	**-**	**+**	**+**	**108**	**33**	**54**	**115**	**21**	**3.80**	**-**
49	**37764**	**45**	**M**	**+**	**35**	**+**	**+**	**+**	**+**	**105**	**31**	**52**	**110**	**22**	**2.20**	**+**
50	**38804**	**44**	**M**	**+**	**10**	**-**		**+**	**+**	**96**	**32**	**48**	**80**	**16**	**2.00**	**+**

KEY WORDS

+ - PRESENT

\- - ABSENT

HE - HEPATIC ENCEPHALOPATHY

HRS - HEPATO RENAL SYNDROME

LDL - LOW DENSITY LIPOPROTEIN

TG - TRIGLYCERIDE

TC - TOTAL CHOLESTEROL

HDL - HIGH DENSITY LIPOPROTEIN

LDL <100 - LOW VALUE

TC<140 - LOW VALUE

HDL <40 - LOW VALUE

ABBREVIATIONS

ACTH	**- Adrenocorticotropic Hormone**
ATP	**- Adenosine Tri Phosphate**
CTL	**- Cytotoxic T Lymphocytes**
DNA	**- Deoxy Ribose Nucleic Acid**
ESR	**- Erythrocyte Sedimentation Rate**
FFA	**- Free Fatty Acids**
HBV	**- Hepatic B Virus HCC**
HCV	**- Hepatic C Virus**
HDL	**- High Density Lipoprotein**
HSC	**- Hepatic Stellate Cells**
INR	**- International Normalized Ratio**
IUB	**- International Union of Biochemistry**
IPAUC	**- International Union of Pure and Applied Chemistry**
KCL/gm	**- kilocalories / gram**
Kg	**- Kilogram**
KOH	**- Potassium Hydroxide**
LCAT	**- Lecithin Cholesterol Acyl Transferase**
LDL	**- Low Density Lipoprotein**

LFT	**- Liver Function Test**
LPS	**- LipoPolySaccharide**
Mg	**- Milligram**
mg/dl	**- milligram/ deciliter**
NADH	**- Sodium Adenosine Dioxide**
NAOH	**- Sodium Adenosine Hydroxide**
NEFA	**- Non-Esterified Fatty Acids**
NSAID	**- Non-Steroidal Anti Inflammatory Drug**
PT	**- Prothrombine Time**
ROS	**- Reactive Oxygen Species**
RBC	**- Red Blood Cells**
SBP	**- Spontaneous Bacterial Peritonitis**
TC	**- Total Cholesterol**
TG	**- TriGlyceride**
UGI	**- Upper Gastro Intestinal**
USG	**- Ultrasonography**
VEGF	**- Vascular Endothelial Growth Factor**
VLDL	**- Very Low Density Lipoprotein**
%	**- Percentage**
µm	**- Micrometer**

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .S.KUMARESAN** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of Participant

LIST OF FIGURES

LIST OF TABLES