# ASSOCIATION OF HIGH SERUM URIC ACID LEVELS IN CHRONIC LIVER DISEASE

Dissertation submitted to

**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**

In partial fulfilment of the regulations

For the award of the degree of

**MD GENERAL MEDICINE**

**TIRUNELVELI MEDICAL COLLEGE & HOSPITAL**

**TIRUNELVELI**


**THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY**

**CHENNAI, TAMIL NADU**

**APRIL 2015**

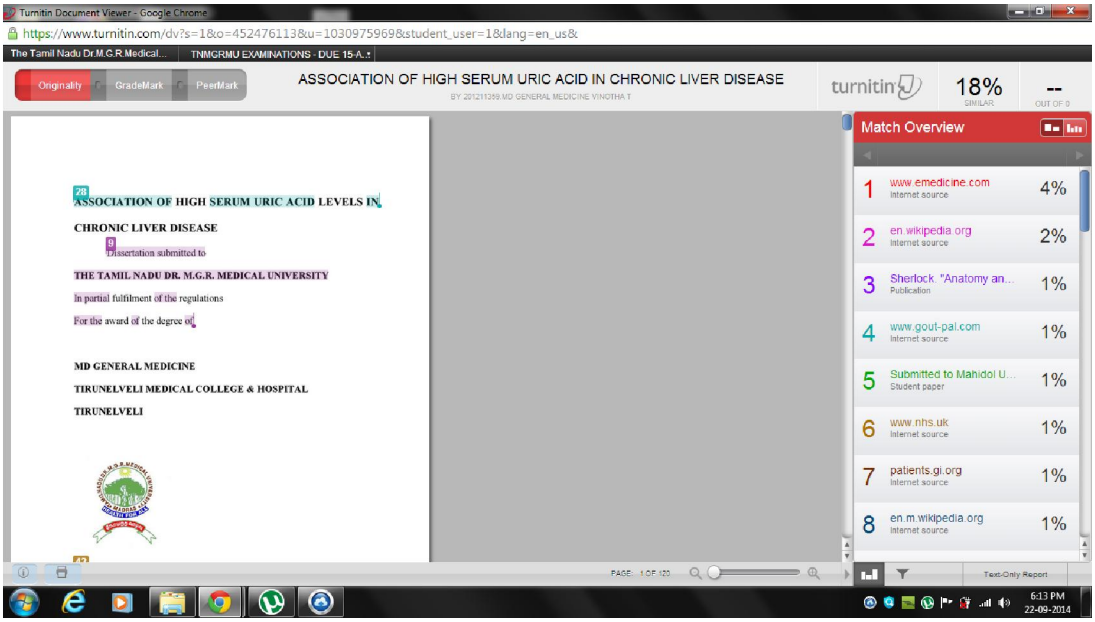
## CERTIFICATE

This is to certify that the dissertation titled **"ASSOCIATION OF HIGH SERUM URIC ACID LEVELS IN CHRONIC LIVER DISEASE"** submitted by Dr.T.VINOTHA to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai, in partial fulfilment of the requirement for the award of M.D. degree Branch I (General Medicine) is a bonafide research work carried out by her under my strict supervision and guidance.

**Dr.M.PAULRAJ,Bsc, M.D.**
Professor of Medicine,
Department of General Medicine,
Tirunelveli Medical College,
Tirunelveli.

**Dr.M.R.VAIRAMUTHURAJU M.D.**
Professor and Head of the
Department of Medicine,
Tirunelveli Medical College,
Tirunelveli.

**DR. L.D.THULASIRAM MS(ORTHO)**
The Dean,
Tirunelveli Medical College,
Tirunelveli.


Turnitin Document Viewer - Google Chrome
https://www.turnitin.com/dv?s=1&o=452476113&u=1030975969&student_user=1&lang=en_us&
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 15-A...
Originality
GradeMark
PeerMark
ASSOCIATION OF HIGH SERUM URIC ACID IN CHRONIC LIVER DISEASE
turnitin
18%
SIMILAR
--
OUT OF 0
ASSOCIATION OF HIGH SERUM URIC ACID LEVELS IN
CHRONIC LIVER DISEASE
Dissertation submitted to
THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY
In partial fulfilment of the regulations
For the award of the degree of
MD GENERAL MEDICINE
TIRUNELVELI MEDICAL COLLEGE & HOSPITAL
TIRUNELVELI
Match Overview
1 www.emedicine.com Internet source 4%
2 en.wikipedia.org Internet source 2%
3 Sherlock, "Anatomy an... Publication 1%
4 www.gout-pal.com Internet source 1%
5 Submitted to Mahidol U... Student paper 1%
6 www.nhs.uk Internet source 1%
7 patients.gi.org Internet source 1%
8 en.m.wikipedia.org Internet source 1%
PAGE: 1 OF 100
Text-Only Report
6:13 PM
22-09-2014

# TIRUNELVELI MEDICAL COLLEGE

**INSTITUTIONAL RESEARCH ETHICS COMMITTEE**

TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

**CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC** REF NO: 409/GM/2013/29.03.13

PROTOCOL TITLE: A Study of Association of High Uric Acid Levels in Chronic Liver Disease

NAME OF PRINCIPAL INVESTIGATOR: T.Vinotha

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

*Dear Dr* T.Vinotha, *the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013.

**THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED**

| | | |
|---|---|---|
| 1. | TIREC Application Form | ☐ |
| 2. | Study Protocol | ☐ |
| 3. | Department Research Committee Approval | ☐ |
| 4. | Patient Information Document and Consent Form in English and Vernacular Language | ☐ |
| 5. | Investigator's Brochure | ☐ |
| 6. | Proposed Methods for Patient Accrual Proposed | ☐ |
| 7. | Curriculum Vitae of the Principal Investigator | ☐ |
| 8. | Insurance /Compensation Policy | ☐ |
| 9. | Investigator's Agreement with Sponsor | ☐ |
| 10. | Investigator's Undertaking | ☐ |
| 11. | DCGI/DGFT approval | ☐ |
| 12. | Clinical Trial Agreement (CTA) | ☐ |
| 13. | Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) | ☐ |
| 14. | Clinical Trials Registry-India (CTRI) Registration | ☐ |

**THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS**

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

**STANDS APPROVED UNDER SEAL**

**Dr.K.Shanmugasundaram MD**
**Registrar, TIREC**
**Tirunelveli Medical College, Tirunelveli – 627011**
**State of Tamilnadu, South India**

**Dr.V.Ramakrishnan MD DM**
**Member Secretary, TIREC**
**Tirunelveli Medical College, Tirunelveli – 627011**
**State of Tamilnadu, South India**

## DECLARATION

I, **DR. T.VINOTHA**, solemnly declare that this dissertation titled **"ASSOCIATION OF HIGH SERUM URIC ACID LEVELS IN CHRONIC LIVER DISEASE"** is a bonafide work done by me at Tirunelveli Medical College from September 2013 to September 2014 under the supervision and guidance of my unit chief, **Prof. Dr.M.PAULRAJ ,Bsc M.D.,** Professor of Medicine.

This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University, towards partial fulfilment of regulation for the award of M.D. degree in General Medicine.

PLACE : TIRUNELVELI (DR.T.VINOTHA)

DATE :

## ACKNOWLEDGEMENT

I take immense pleasure in acknowledging all those who helped me to make this dissertation a reality.

I thank our dean, **Dr.L.D.THULASIRAM**,**M.S(ORTHO)** Tirunelveli Medical College for allowing me to avail the facilities needed for my dissertation work.

I express my sincere heartfelt gratitude to our beloved Professor and Head of the Department of General Medicine, **Dr.M.R.VAIRAMUTHU RAJU M.D**., for having approved this study and for his valuable guidance.

I express my profound sense of gratitude to our beloved unit chief, Prof.**Dr.M.PAULRAJ,Bsc, M.D**., for his guidance, motivation and valuable suggestions.

I extend my sincere thanks to our unit senior Assistant Professors, **Dr.G.RATHNAKUMAR M.D.,** and **Dr.S.JAWAHAR M.D.,** for their invaluable support and guidance.

I express my gratitude to our assistant Professors of Gastroenterology, Dr.KANDASAMY MD.,D.M .,and Dr.SELVA SEKARAN, M.D., D.M who allowed me to carry out this study in the gastroenterology ward and for their valuable guidance.

I also thank the department of biochemistry for offering me the laboratory support needed for this study.

I also thank Mr Selvaprakasam for his guidance regarding statistics.

I sincerely thank all the patients without whom this study would not have been possible.

I extend my love and gratitude to my family and friends for their invaluable support, guidance and criticisms.

## CONTENTS

# INTRODUCTION

In higher animals and humans the serum uric acid is an end product of purine metabolism, excreted mainly through kidneys. Increased serum uric acid levels was thought to be the main reason for arthritis due to crystal deposition in joints, renal stones and other vascular events.

More recently, increased levels of serum uric acid levels also involved in the future development of hypertension, cardiovascular disease, kidney disease and metabolic syndrome

Although increased serum uric acid levels are involved in the development of many diseases the following mechanisms included as a cause, they are dysfunction of endothelium, resistance to insulin, systemic inflammation and oxidative stress.

Several biological studies shown that increased serum uric acid level have been found to correlate directly with the level of tissue injury .Compared to the serum levels of uric acid, tissue levels of uric acid has better prediction of tissue injury. So serum uric acid may be considered as an indicator of tissue injury

Recent studies on serum uric acid have shown an increased serum uric acid levels associated with the development of steatosis of liver in the patients who had Non-Alcoholic fatty Liver Disease (NAFLD) after adjustment for various features of metabolic syndrome. It is proposed that the role of increased uric acid levels in the pathogenesis of liver disease thought to be due to its pro-inflammatory effects, for

example, increased levels of uric acid is considered as an important marker in the pathogenesis of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steato hepatitis (NASH).

Addition to this, hyperuricemia involved in the progressive development of hepatitis C virus related disease and liver diseases due to excessive consumption of alcohol. This strongly suggests that increased uric acid levels, strongly reflects and even causes an increased oxidative stress, resistance to insulin and inflammation in the systemic circulation. This become one of the main risk factors for future development of cirrhosis of liver or hepatic inflammation due to necrosis both in alcoholic and non-alcoholic

Oxidative stress in liver mainly caused by the mitochondrial dysfunction, and also by proinflammatory cytokines like tumor necrosis factor alpha (TNF) are thought to play a very important role in the progression of liver cell damage in cases of nonalcoholic fatty liver disease

NAFLD not only directly leads to the development of liver failure and hepatocellular carcinoma, but also is involved in the future development of type 2 diabetes and cardiovascular diseases due to atherosclerosis. NAFLD is complex disease and nowadays it is challenging for the human health.

In chronic liver disease due to various causes uric acid levels are found to be increased .Most of the people with nonalcoholic fatty liver disease, the increased uric acid levels are implicated as an important etiological risk factor. Also increased

uric acid level has a known effect on alcohol metabolism, hyperuricemia also be found in patients with alcoholic liver disease.

Recent cross-sectional studies showed that increased serum uric acid levels are reasonably increased in NAFLD and also the prevalence rate of NAFLD increases as the serum uric acid levels increases.

These results concluded that elevated serum levels of uric acid may be associated with the development of nonalcoholic fatty liver disease. However, whether this association of serum uric acid and liver disease is causal, a by stander, or a consequence of NAFLD still remains under debate

## AIM OF THE STUDY

- To assess the prevalence of hyperuricemia in nonalcoholic patients with cirrhosis liver and fatty liver
- To study the association of uric acid and various risk factors
- To study the usefulness of serum uric acid as an prognostic marker in chronic liver disease

# REVIEW OF LITERATURE

## ANATOMY OF THE LIVER

It is the largest intra abdominal organ in the body. It weighs about 1200 gms to 1500gms and also it comprises one fifteenth of the body total weight in the adult. It is relatively larger in size in infancy and childhood compared to adults and measures about one eighteenth of the total birth weight.

Liver present and occupies in the right hypochondriam and epigastric region of upper abdomen. liver is a wedge shaped organ and capsule of the liver plays an important role in maintaining the liver integrity. Liver is covered by the chest ribs in the upper quadrant on the right side of abdomen hence the upper border of the human liver lies nearly at the level of the right side nipple.

The liver anatomy describes liver in to right and left lobes, the external appearance of liver division into two lobes is by umbilical fissure and a ligament called falciform . The right lobe is much larger than left side lobe of liver, it is six times larger than the left lobe of liver. The caudate lobe is seen in the posterior surface of right lobe of liver and the lobe in the inferior surface of liver is known as the quadrate lobe. The two lobes of the liver are also separated anteriorly by a visible fold of peritoneum which is named as

the falciform ligament. Liver is a divided posteriorly by ligamentum venosum a fissure in liver and also inferiorly by the fissure called ligamentum teres.

**Surfaces of liver**

The liver has superior, anterior, right, posterior and inferior surfaces, and a distinct Inferior border, the superior, anterior and right surfaces of the liver are continuous and there is no definite borders to separate them. The borders are rounded between the right and inferior surfaces, but they angled more sharply between the anterior and inferior surfaces. This part of the inferior border of liver is notched by the ligamentum teres. The inferior border present in the right costal margin lateral to the gallbladder fundus. In the left side of the ligamentum teres, the inferior border ascends below the right costal margin.

It crosses the infrasternal angle and passes behind the medial end of the left costal margin. At the infra sternal angle of body the lower border of the liver is in relation to the muscles of anterior abdominal wall and it can be very well examined by percussion.

In the midline of human body, the inferior border of the liver lies near the Trans pyloric plane and about a hand's breadth below the xiphi sternal joint.

**Superior surface**

It is the largest surface and it lies just below the Diaphragm and separated from it by the peritoneum except for a small triangular shape area. Most of the superior surface of liver lies below the right dome of diaphragm. The left side of the superior surface of liver lies near part of the left dome of the diaphragm. This surface blends with the anterior, posterior and right surfaces over the 'dome' of the liver.

**Anterior surface**

This surface is approximately triangular and convex in shape and covered by peritoneum except at the level of attachment of the falciform ligament. Most of this is in contact with the anterior attachment of the diaphragm. In the right side the diaphragm separates this surface from the pleura, 6 th to 10 th ribs and costal cartilages, and on the left side of the liver from the seventh & eighth inter costal cartilages. The median part of the anterior surface of the liver lies behind the xiphoid process and the anterior abdominal wall.

**Right surface**

The right surface of the liver is covered by peritoneum and it lies near the right dome of the diaphragm. Above and lateral to the upper third of the right surface, lies the right lung and basal pleura. The diaphragm,

costodiaphramatic recess and the ninth and tenth ribs lie lateral to the right surface

**Blood supply of the liver**

The liver has a dual blood supply. The portal vein which is formed by joining superior mesenteric vein and splenic vein drain venous blood both from the intestines and spleen, it is a special system called portal system. Hepatic artery which arises as a branch from the celiac trunk or axis supplies blood to the liver ,it is the main arterial supply of pure blood to liver.

These two PV and hepatic artery gains into the liver via a fissure in Rt lobe. Inside the liver porta hepatis, there are divisions of the portal vein and the hepatic artery into small branches which ultimately supplies both the lobes of liver

**Nerve supply of the liver**

The sympathetic ganglia T7 to T10 has nerve fibers which supplies the liver via hepatic plexus, which in turn has synapses in the celiac plexus, the left vagus and right vagus nerves and the right phrenic nerve.

**Venous drainage of liver**

The main venous drainage of the liver is from hepatic vein which originates from liver as left and right hepatic veins then drain into the

inferior vena cava, this right and left hepatic vein carries impure blood to right atrium via IVC (inferior vena cava)

**Lymphatic drainage of the liver**

Lymphatic drainage of liver is usually to the node in the porta hepatis, which is seen along the blood vessel, some lymphatics also enter the mediastinum through falciform ligament and some lymphatics also enters thorax via inferior vena cava.

**DEVELOPMENT OF THE LIVER**

The formation of liver is by endodermal bud which begins from the foregut, during the third or fourth week of pregnancy. This endodermal bud separated into two parts as hepatic part and biliary part. The hepatic part of the liver contains basic progenitor cells which will differentiates into hepatocytes or ductal cells in the formation of liver, which later develops into the early primitive bile duct structures. .

Changes of microscopic part of cells is associated with changes in the cytokeratin structure inside the cell.

The relation between proliferating cell mass in endodermal region, foregut and endodermal bud result in the formation of the gallbladder and extra hepatic biliary ducts. Bile is produced in the liver of foetus at about the

twelfth week of gestation. The haemaetopoietic cells are acquired from the septum transversum mesoderm in foetal liver, the kuffer cells and connective tissue cells also develops. The major haemopoietic function in foetus is by the liver but in adults it is taken over by bone marrow, the haematopoietic function of liver is grossly reduced during the intrauterine life at later stages that is during last two months.

**HISTOLOGY OF LIVER**

The liver contains two types of tunnels, they are the portal canal and the hepatic central canal. These canals are arranged in a way, that they will not touch each other.

The sinusoids placed haphazardly, usually in perpendicular direction to the lines connecting the central veins of the liver. The central hepatic canals contain radicles of the hepatic vein, which are surrounded by a limiting plate of cells. The portal triad formed by the portal vein radicle, the hepatic arteriole and the bile duct.

The liver cells comprises about 60% of the liver parenchyma. They are polygonal in shape and nearly 30 μm in diameter. It has a single nucleus mostly they multiply by mitosis.

The wall in the sinusoids composed of endothelial cells and phagocytic cells from reticulo endothelial system. The flat components in the liver are

known as Kupffer cells and they play an important role in the formation of immune bodies, phagocytosis and blood formation.

The tissue space in between the hepatocytes and the sinusoidal lining cells are called as space of disse. It contains fluid, which flows away and into the lymphatics present in the portal triads.

**Electron microscopy:**

Under the electron microscopy the cells of the liver looks straight except for a few anchoring pegs. From the hepatocytes the microvilli protrudes into the wall of the biliary canaliculi. Along with the sinusoidal border of the liver, the irregular sized microvillus projects into the peri-sinusoidal space .The nucleus contains deoxy ribonucleoprotein.

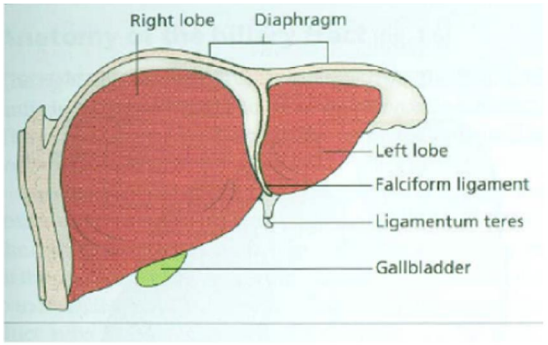
The mitochondria also has got two types of membranes. The inner membrane is invaginated and form grooves or cristae. More amount of energy giving processes takes place inside them particularly those involved in oxidative phosphorylation.

The rough endoplasmic reticulum are seen as lamellar profiles which are lined by the ribosomes. They produces specific proteins, mainly albumin which are used in coagulation of blood and enzymes. Triglycerides are formed from the free fatty acids and joins with the proteins and secreted by exocytosis as lipoprotein.

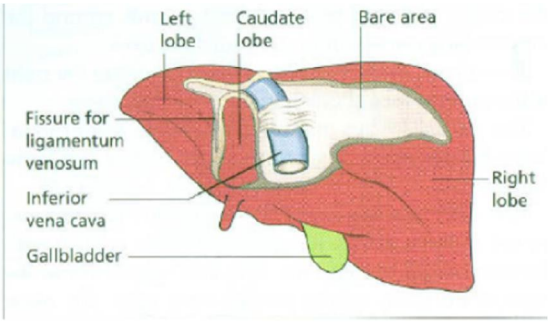
The smooth endoplasmic reticulum of the liver forms tubules and vesicles which contains microsomes. It is also a site for conjugation of bilirubin and detoxification of many of the drugs and other compounds. Steroids are synthesized in this part of liver.

The lysosomes in liver are pericanalicular dense bodies present near bile canaliculi. They are also called as intracellular scavengers. The golgi apparatus has a system of particles and the vesicles which also lies along the canaliculus.

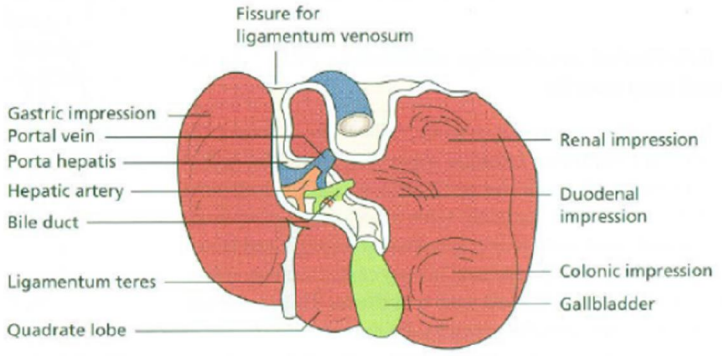
The sinusoidal wall consists of three types of cells. They are endothelial cells, kupffer cells and lipocytes. The lipocytes present in the space of disse between the hepatocytes and endothelial cells. The kupffer cells are elongated structures having irregular outline, with crenated nucleus, few mitochondria and varying numbers of lysosomes. Pit cells are found in the sinusoidal wall they contain granules and may have an endocrine function.



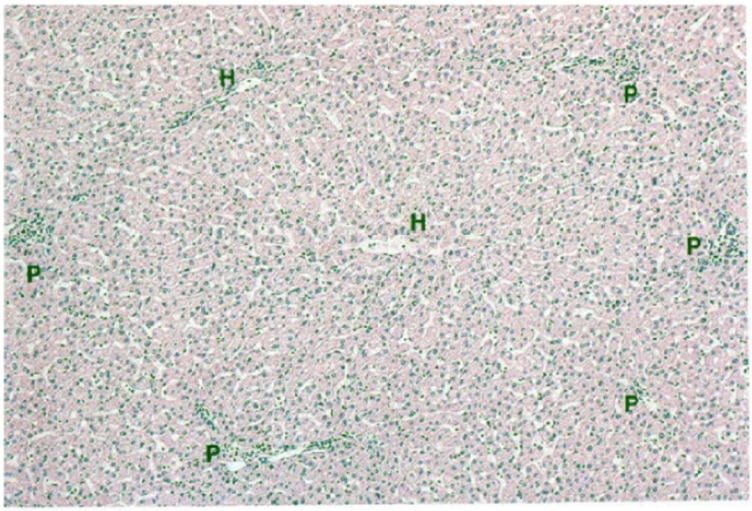

**Anterior view of the Liver**




**Posterior view of the Liver**




**Inferior view of the Liver**




**Normal hepatic histology. H, Terminal hepatic vein; P, Portal tract**

Liver is one of a complex organ present in our body which has an interdependent metabolic, excretory and defense functions in our body. Many screening tests are used for detection of hepato-biliary abnormalities and also helps to differentiate clinically suspected disease and assess the severity of liver disease

## CHRONIC LIVER DISEASE

Chronic diseases of liver can be defined as a process of disease results in progressive destruction of liver and also liver parenchymal regeneration resulting in fibrosis leading to liver fibrosis and liver cirrhosis.

Because of long duration of insult to the liver, scar tissue develops gradually and Changes the normal functioning liver tissue and slowly diminishes blood supply via the liver.

When the original liver tissue and function is lost, the metabolism of nutrients, hormones, drugs, and poisons are processed ineffectively by the liver .In alcoholic patients the leading cause of death is due to CLD. Chronic liver disease occurs both in alcoholic and nonalcoholic patients.

### Alcoholic liver disease

Abuse of Alcohol is present worldwide. Increased alcohol intake not only affects the physical, mental health but also affects the financial state of

the people. Alcoholic liver disease is one of the leading cause of death nowadays. Most of the patients with advanced disease die within 48 months

## PATHOPHYSIOLOGY OF ALCOHOLIC LIVER DISEASE

Alcohol can produce a wide range of liver diseases from fatty change to hepatitis and later cirrhosis.

### Fatty change in liver

The metabolism of alcohol in liver invariably produces fat in the liver cells, mainly in zone 3. This changes are minimal with small amounts of alcohol. With larger amounts of alcohol intake the cells become swollen with fat (steatosis) giving a Swiss-cheese effect on staining with haematoxylin and eosin.

Steatosis of liver also seen in case of obesity, diabetes, starvation and occasionally in chronic illness. There is no damage to liver cells. The fat in the liver cells disappears after stopping alcohol.

In some cases of fatty liver collagen is deposited around the central hepatic veins (perivenular fibrosis) and this can progress later to development of cirrhosis without a previous hepatitis.

Alcohol has direct effect on stellate cells, which transforms them into collagen-producing myofibroblast cells. Cirrhosis may later develop if there is an imbalance between degradation and production of collagen in liver

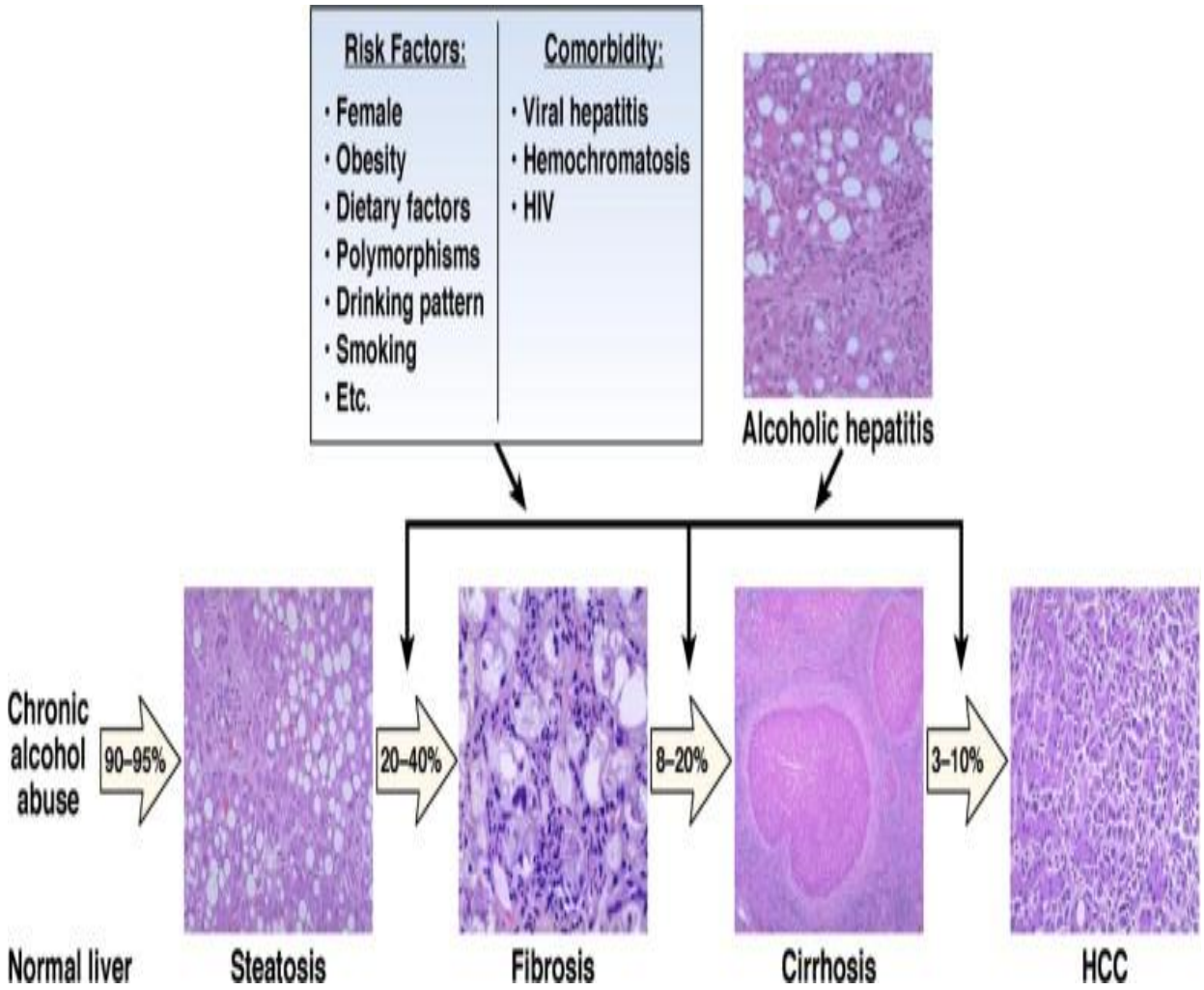
**Alcoholic hepatitis**

In addition to fatty change in liver there is infiltration by polymorphonuclear leucocytes and hepatocyte necrosis seen mainly in zone 3. Dense cytoplasmic inclusions which are called as Mallory bodies are sometimes seen in the hepatocytes and giant mitochondria are also seen.

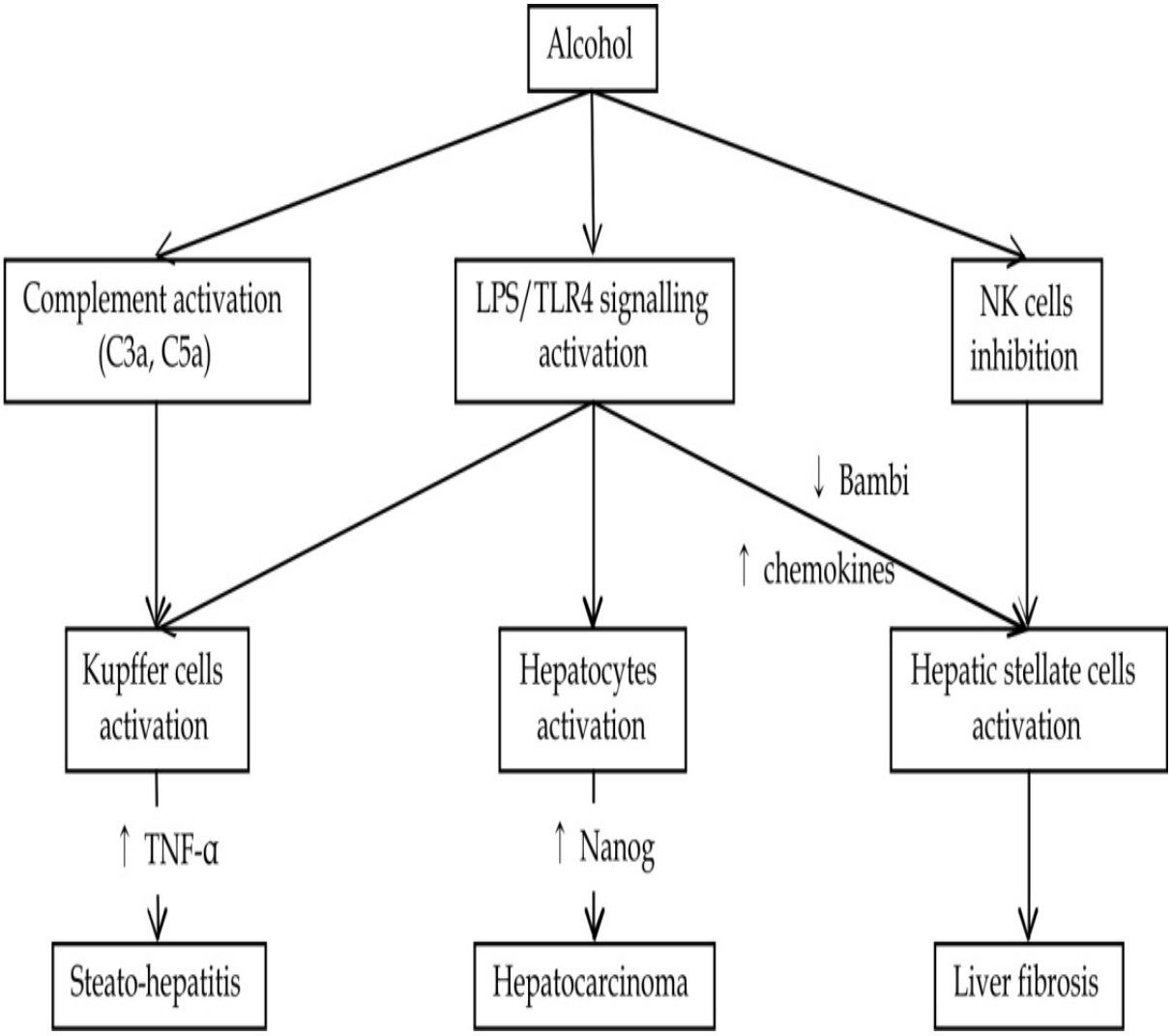
Mallory bodies are only suggestive of, but are not specific for, alcoholic damage as they can be seen in other liver diseases, such as Wilson's disease and PBC. If alcohol consumption continues for longer period, alcoholic hepatitis later progress to cirrhosis

**Alcoholic cirrhosis**

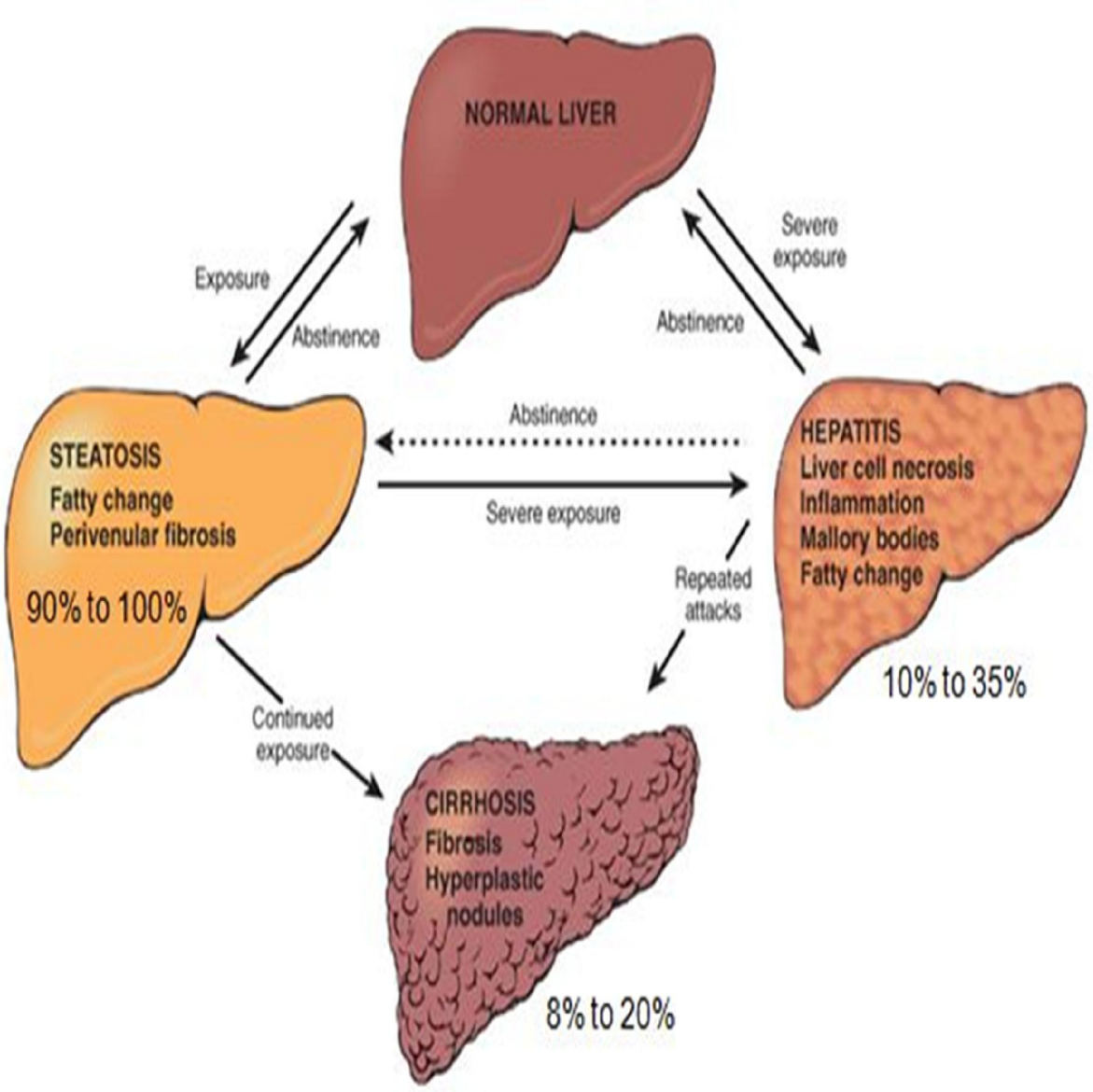
This is classically of the micronodular type, but can present with a mixed pattern .it may also be seen with accompanying fatty change, and evidence of pre-existing alcoholic hepatitis in liver


Risk Factors:
• Female
• Obesity
• Dietary factors
• Polymorphisms
• Drinking pattern
• Smoking
• Etc.
Comorbidity:
• Viral hepatitis
• Hemochromatosis
• HIV
Alcoholic hepatitis
Chronic alcohol abuse
90–95%
20–40%
8–20%
3–10%
Normal liver
Steatosis
Fibrosis
Cirrhosis
HCC

## MECHANISM OF LIVER CELL INJURY



## STAGES OF ALCOHOLIC LIVER DISEASE



## URIC ACID IN ALCOHOLIC LIVER DISEASE

Increased intake of alcohol (ethanol) is associated with a significant rise of serum uric acid, which has a dual action. Serum uric acid and alcohol are associated by many mechanisms. Alcohol increases the formation of serum levels of UA in liver by increasing the metabolic production of body lactic acid and later causes 'lacticacidosis'.

The plasma concentrations of xanthine and hypoxanthine are increased by alcohol because of increased degradation of adenine nucleotide which is a weak inhibitor of the enzyme xanthine dehydrogenase. Beer also has contribution to purines. Ethanol decreases excretion of uric acid by promoting dehydration and rarely result in clinical ketoacidosis.

## NON ALCOHOLIC FATTY LIVER DISEASE

### NATURAL HISTORY

Overall, morbidity and mortality significantly and definitely higher in NASH patients compared to general population, in NASH patients most commonly death is due to Coronary artery disease and malignancy, next common is liver related mortality. There is significantly shorter survival in nonalcoholic steato hepatitis children compared to people in general

population with NASH, The NAFLD natural history is determined mostly by the severity of the histologic damage and histologic severity.

Mostly benign clinical course is seen in NAFLD patients having pure steatosis in liver without inflammation and they usually have a benign course. Patients over a period of 10 to 21 years about15 to 20% of all NASH patients will progress to cirrhosis related complications.

When initial biopsy of liver is taken for NASH patients one-third will be having advanced hepatic fibrosis and another 9% to 15% will have quite well established cirrhosis, In patients with NASH, the major risk factor in the development of hepatocellular carcinoma (HCC) is cirrhosis.

The prevalence of hepatocellular carcinoma over a 20 year period in NASH and NAFLD is as follows (a) NAFLD 0% to 0.5 %

(b) NASH 0% to 2.8%

Now more number of cases with NASH-associated cirrhosis are under going

Transplantation of liver

The estimated 5 year and 10 year survival for patients with NASH are 67% and 59 %.But it is very difficult to differentiate the cause of death whether due to liver disease or underlying cause

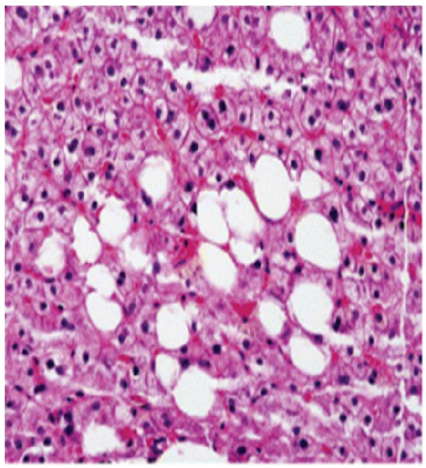
## PATHOPHYSIOLOGY

Even after various studies the pathophysiology of NAFLD is still not clear. The two hit theory implicates both insulin resistance and oxidative stress are potential factors that leads to steatohepatitis , fibrosis and finally cirrhosis.

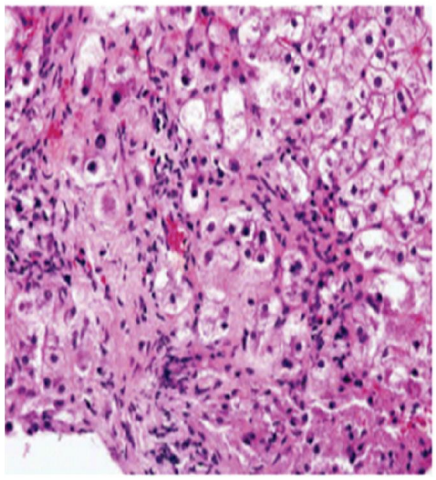
The “first hit” theory is excessive fat accumulation in liver hepatocytes, which is very closely linked to insulin resistance and obesity. In this process, because of increased accumulation of fatty acids steatosis develops. The mechanism by which steatohepatitis develops and progress to fibrosis is not very clear.

The ‘‘second hit’’ theory is the process from oxidative stress to the hepatocyte injury, resulting in inflammation, and fibrosis; SUA has been proved to be pro inflammatory and an increased SUA level reflects the rate of cell turnover.

Mitochondrial injury leads to ATP depletion reactive oxygen species generation, lipid peroxidation and cytokine induction which causes hepatocyte injury. In recent years, some study showed that SUA had strong antioxidant function



Fatty Liver



NASH

Fatty Liver

↓

NASH

↓

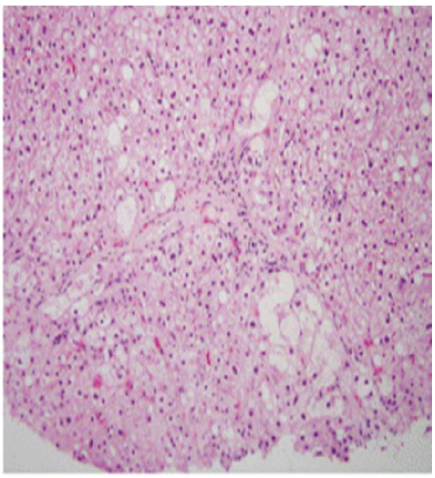
NASH
with Fibrosis

↓

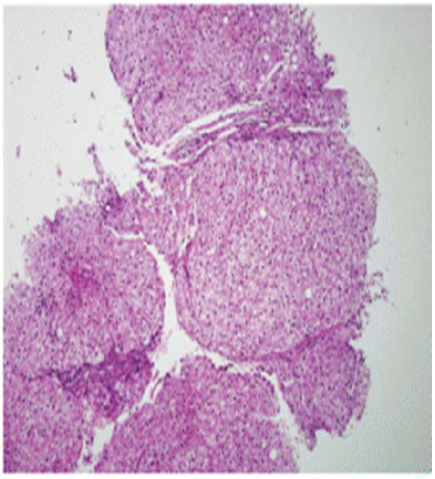
Cirrhosis

↓

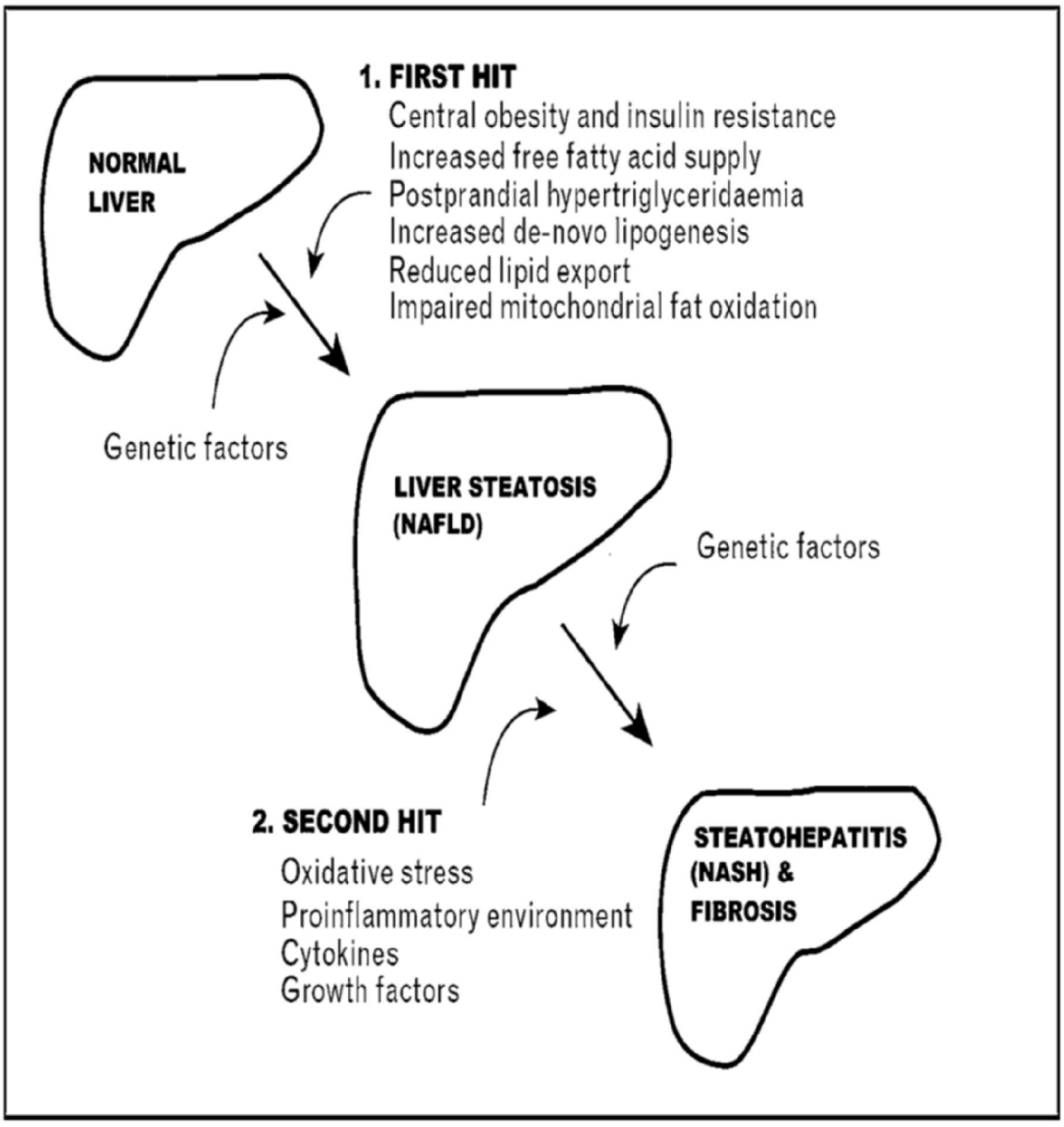
Decompensated
Cirrhosis

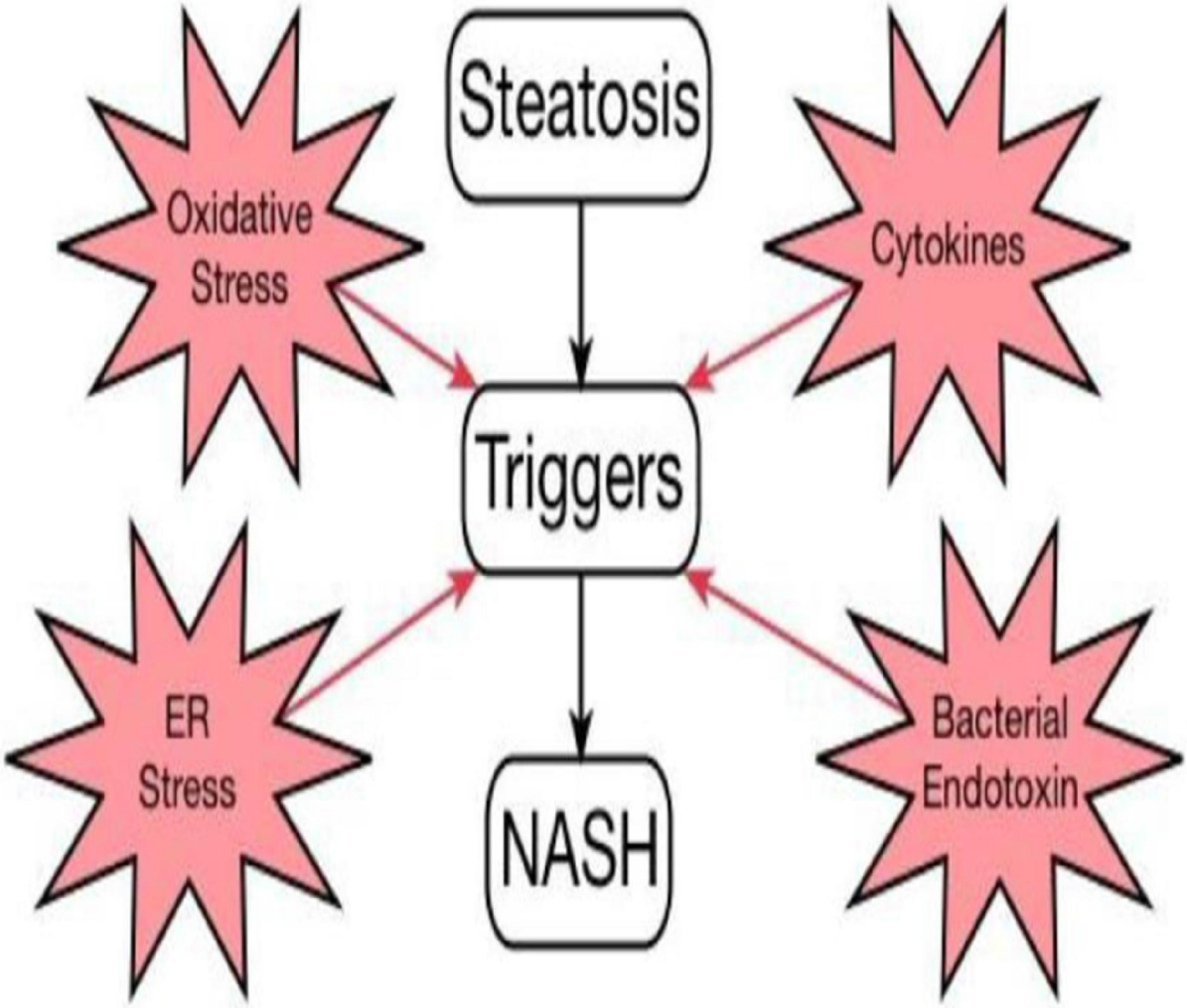


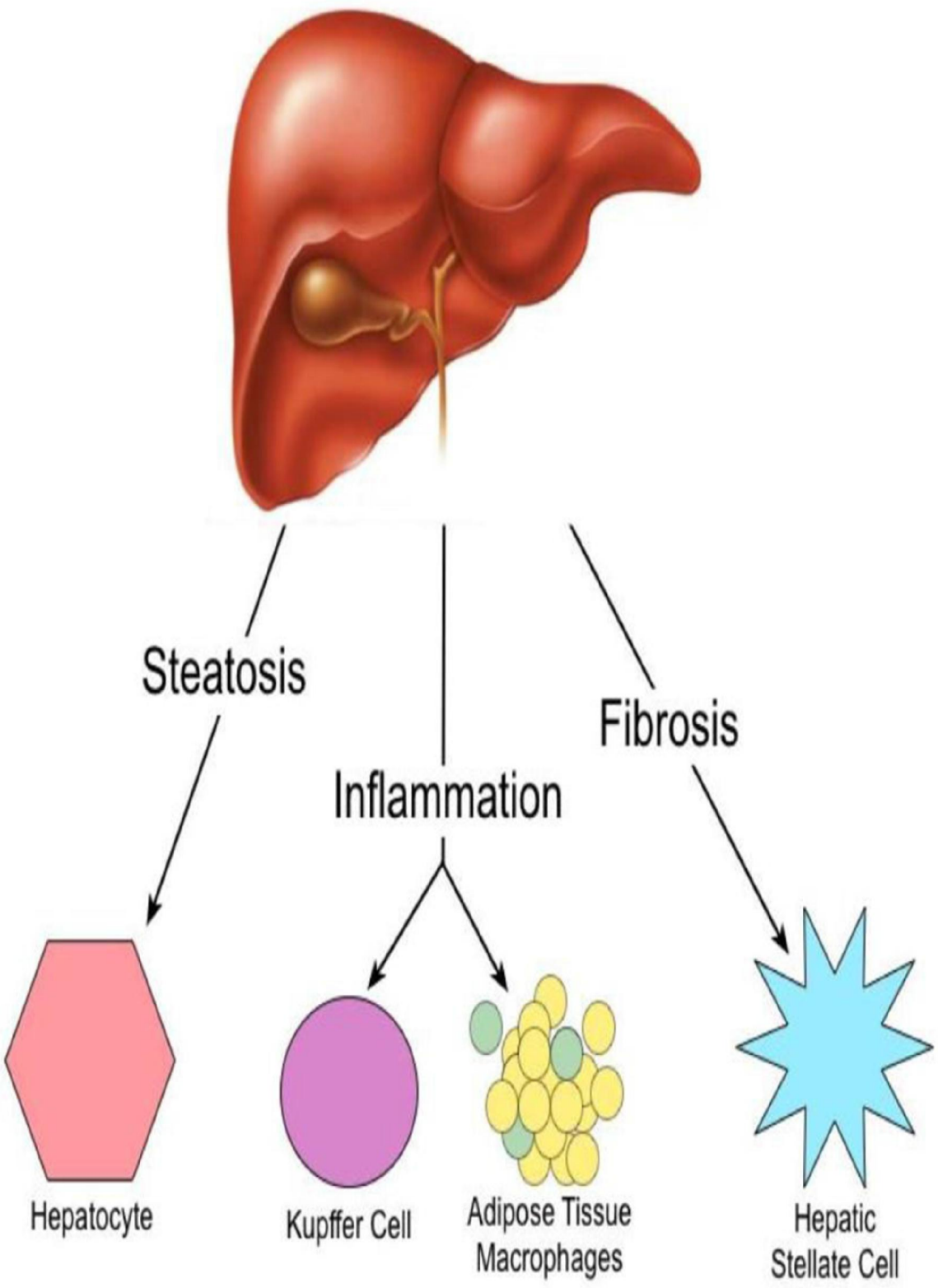
NASH with Fibrosis

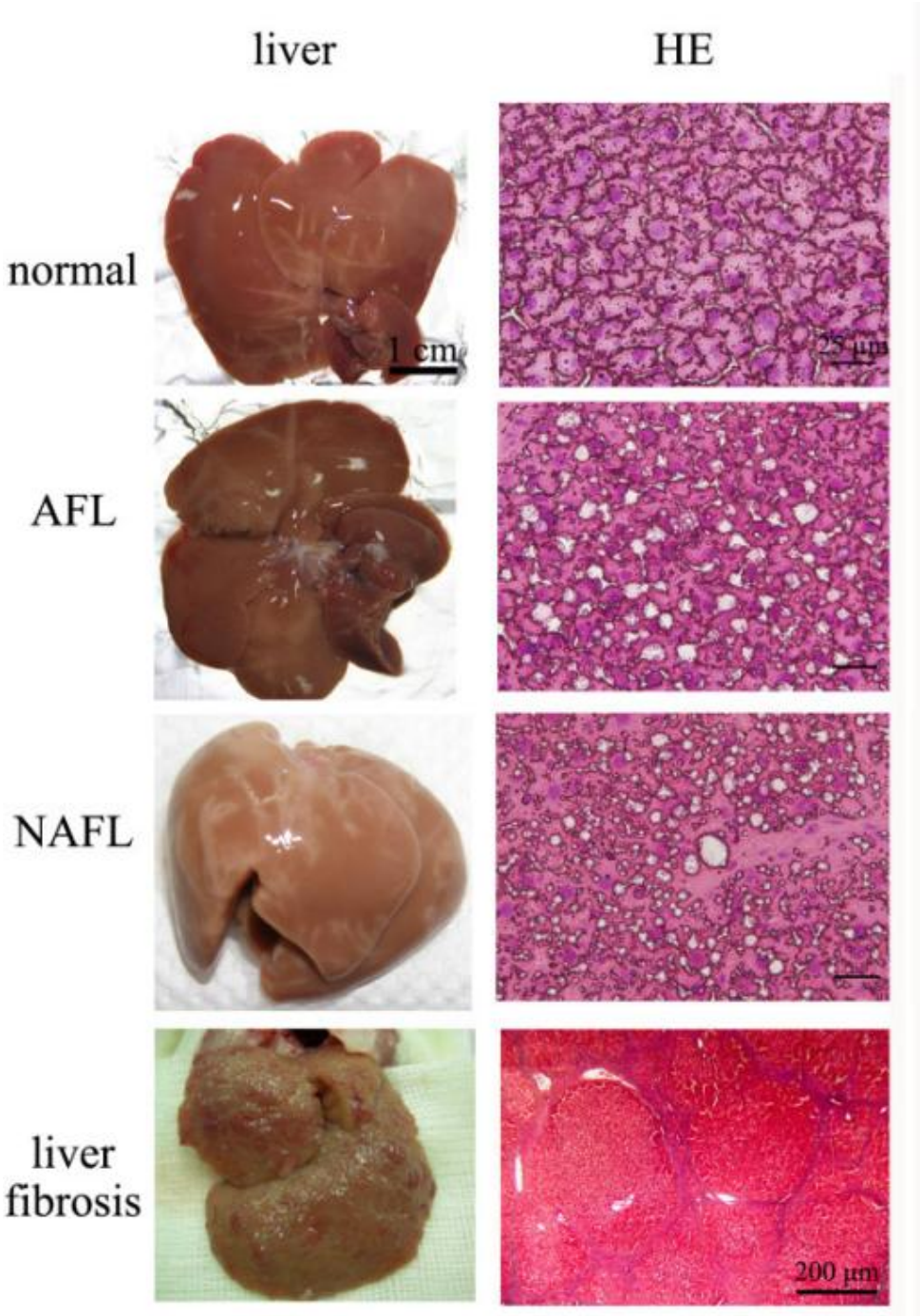


Cirrhosis


1. FIRST HIT
Central obesity and insulin resistance
Increased free fatty acid supply
Postprandial hypertriglyceridaemia
Increased de-novo lipogenesis
Reduced lipid export
Impaired mitochondrial fat oxidation
NORMAL LIVER
Genetic factors
LIVER STEATOSIS (NAFLD)
Genetic factors
2. SECOND HIT
Oxidative stress
Proinflammatory environment
Cytokines
Growth factors
STEATOHEPATITIS (NASH) & FIBROSIS


Steatosis
Oxidative Stress
Cytokines
Triggers
ER Stress
Bacterial Endotoxin
NASH


Steatosis
Inflammation
Fibrosis
Hepatocyte
Kupffer Cell
Adipose Tissue Macrophages
Hepatic Stellate Cell


liver
HE
normal
1 cm
25 µm
AFL
NAFL
liver fibrosis
200 µm

## INSULIN RESISTANCE

Insulin resistance is considered as an important factor in the development of NAFLD. Peripheral insulin resistance causes lipolysis of triglyceride within the adipose tissues and inhibits adipocyte uptake of fatty acids, both in turn, increasing the delivery of fatty acids to the liver.

The compensatory hyperinsulinemia causes promotion of hepatic de-novo lipogenesis and esterification of fatty acids into triglycerides, and also decreases fatty acid oxidation. Hence obesity, which often leads to insulin resistance and presents a fatty challenge to the liver.

Insulin resistance and hyper insulinemia both indirectly associated with development of NAFLD. Insulin resistance index and insulin secretion were Measured using homeostasis model assessment. Patients with NAFLD have fasting and glucose induced hyper insulinemia and insulin resistance.

Insulin resistance and hyper insulinemia causes excess lipolysis which then causes increased levels of free fatty acids. Increased fatty acid uptake leads to overload of mitochondrial beta oxidation and leads to accumulation of fatty acids in hepatocytes.

Due to a suppression of TNF-alpha production and also an antagonism of its function, in that adiponectin and TNF-alpha elicit many opposite

functions, for example, TNF-alpha being a causative factor of insulin resistance, whereas adiponectin increases insulin sensitivity.

Similarly, TNF-alpha is a proinflammatory cytokine, whereas adiponectin has direct anti-inflammatory effects. Although the primary etiology of NAFLD and ALD is different, these liver diseases apparently share similarities in disease progression.

The hepatic consequences of insulin resistance are:

1. Increased lipogenesis via insulin:

    Insulin directly up-regulates the transcription and proteolytic maturation of the transcription factor SREBP-1c. This action is independent of the insulin receptor (IRS-1) that mediates insulin's glucose influence

2. Increased lipogenesis via hyperglycaemia:

The elevated glycaemia directly up-regulates nuclear translocation of carbohydrate responsive element binding protein ( CHREBP). CHREBP acts in synergy with SREBP1c to further inducing the lipogenic gene expression and to provide the precursors for lipogenesis by also inducing glycolytic gene expression

3. Increased NEFA delivery to the liver:

Adipocytes are normally extensively insulin sensitive. Adipocyte insulin resistance results in a reduced suppression of lipolysis, and thus an increased NEFA release into the circulation and hepatic uptake

4. Decreased VLDL excretion:

Insulin attenuates apolipoprotein B, and hence VLDL, formation. This impairs hepatic triglyceride exportation ability. The mechanism behind this frequently observed phenomenon has not been fully determined, though may it occur via microsomal triglyceride transfer protein (MTP) down regulation.

MTP is a critical determinant of triglyceride and apolipoprotein B incorporation into VLDL and its subsequent plasma excretion. MTP-specific inhibition reduces plasma triglycerides and VLDL, whilst increasing hepatic triglycerides

From the above actions it is clear that insulin resistance is a key factor in hepatic lipid balance and steatosis development. When vigorously assessed most non-diabetic NAFLD patients have sub-clinical insulin resistance with evidence of impaired glucose peripheral uptake. Sub-clinical

Systemic and hepatic insulin resistance correlates strongly with intra-hepatic

steatosis. Most NAFLD patients do not have overt systemic insulin resistance i.e. type 2 diabetes, and only around 50% of type 2 diabetics have NAFLD

## OXIDATIVE STRESS

It is unclear why only some patients develop NAFLD alone and others develop hepatic fibrosis and cirrhosis. Mitochondria is thought to be the major source of reactive oxygen species which leads to development of steatohepatitis through lipid peroxidation and cytokine induction.

Mitochondrial swelling and damage results in impaired ATP resynthesis and depletion of ATP. Inflammation and hepatocyte damage also causes recruitment of inflammatory cells, induction of cytokine and generation of reactive oxygen species from neutrophils and macrophages.

One of the most advocated mechanisms that could explain why alcohol and obesity, potentiate each other in progression from fatty liver to steatohepatitis and fibrosis, is oxidative stress.

Although some degree of oxidative stress can be seen in the steatosis of most etiologies. It is believed that an alternative or extra source of oxidative stress is needed to escape the cellular defense systems and to progress from a fatty liver.

Insulin resistance has been suggested as being capable of playing the roles of both the first and the second hit, as it often leads to fatty liver, which further decreases insulin sensitivity.

The connections between insulin resistance, steatohepatitis and oxidative stress have been supported by the observations that individuals with NASH are significantly more insulin resistant than those with a fatty liver alone and the oxidative damage is more pronounced in NASH than in simple steatosis

Non-alcoholic fatty liver disease (NAFLD) is a very quiet common disorder and includes a group of conditions results in increased hepatic fat accumulation in the absence of significant alcohol consumption the causes are like viral infection, some diseases causing some specific changes to liver pathology.

Nonalcoholic fatty liver disease commonly causes chronic liver disease, which has many etiological factors like genetic, environmental, metabolic, and stress-related components. The most common form of NAFLD is called as fatty liver. In fatty liver, accumulation of fat occurs in the liver cells.

A small group of people with non-alcoholic fatty liver disease may develop a more serious condition named Non-alcoholic steatohepatitis

(NASH). In NASH, accumulation of fat is associated with inflammation of liver cells and varying amount of scarring.

NASH is a very serious condition which may leads to severe liver damage and cirrhosis. Cirrhosis occurs when the liver damage is extensive and the liver cells are slowly replaced by scar tissue which makes the liver unable to function properly. The microscopic picture of NAFLD is much more similar to liver disease that is produced due to increased alcohol intake.

NAFLD is associated more commonly with obesity, insulin resistance, dyslipidemia and metabolic syndrome. NAFLD has clinical important because of its increasing prevalence throughout the world and it's potential to progress to advanced cirrhosis and hepatic failure

In recent years, many studies shows an association between elevated serum uric acid concentrations and its association with further development of chronic liver disease in patients with NAFLD has been reported .

Some people concluded that increased uric acid level is an independent risk factor for the development of NAFLD, and is also related to its histologic severity.

Identifying the risk factors is very much essential for the prevention of development of NAFLD. The development of NAFLD has various levels of physiologic and biochemical stages, which includes genetic, environmental,

metabolic, and stress-related factors. The exact risk factors for the development of NAFLD in not yet identified properly.

NAFLD also considered as a part of metabolic syndrome. Recent researches are focusing on many factors that contribute to the future development of NASH.

Some of the risk factors are Oxidative stress, production and release of toxic inflammatory proteins like cytokines by the patient's own inflammatory cells, liver cells, or fat cells which later causes necrosis of liver cell or death.

**EPIDEMIOLOGY OF NAFLD**

NAFLD becoming one of the most prevalent liver diseases affecting people in Western countries. Now a days, this disease affects 20%–30% of the general population approximately.

NAFLD is one of the emerging problems affecting people in the Asia-Pacific region and the prevalence is increasing gradually. Simple fatty liver is generally a benign condition, but when it leads to development of NASH in these patients later it can progress to the development of cirrhosis of liver and liver failure and the 5-year survival rate in these patients approximately ranges about 67%.

Non-alcoholic fatty liver disease (NAFLD) is a main cause of development of chronic liver disease throughout the world. NAFLD prevalence in Indian population ranges from 5 to 28%, which is comparable to the West.

Compared to the West, Indians develop NAFLD at lower degree. Because of the change of lifestyle and diet structure, increased incidence of NAFLD has become a very serious public health problem in the world. It is not only a major killer in western countries, but also the serious health problem in Asia.

Present in approximately 20 to 30 % of patients in western countries and in Asia it is around 12 to 24%. But the exact prevalence of this disease is not known which may be higher than this.

The most common cause of abnormally elevated liver enzymes in patients who has asymptomatic liver disease is NAFLD. NAFLD most commonly seen in fifth or sixth decade of patients. It also associated with other diseases like diabetes mellitus, obesity and dyslipidemia.

Nonalcoholic fatty liver disease is most commonly seen among men than women in all age groups up to the age 60 years. This is because of the protective nature of estrogen.

**GRADING OF NAFLD**

GRADE 1: MILD

Steatosis-mostly as macro vesicular

Ballooning-occasionally seen in zone 3

Inflammation of the lobules-mild acute and chronic inflammation with neutrophils and monocytes respectively inflammation of the portals-ranges from none to mild

GRADE 2: MODERATE

Steatosis -any degree, mixed

Ballooning-in zone 3

Lobular inflammation-neutrophils maybe associated with ballooned hepatocytes with or without inflammation

Inflammation of the portals- ranges from mild to moderate

GRADE 3: SEVERE

Steatosis-greater than 66%.mixed

Ballooning-marked. Predominantly in zone 3

Lobular inflammation-scattered acute and chronic inflammation

Portal inflammation-mild to moderate

STAGING

Requires Masson trichrome or equivalent stain

Stage 1:

perivenular, perisinusoidal or pericellular fibrosis in zone 3

fibrosis maybe focal or extensive.

Simple fatty liver (steatosis). Here increased amount of fat globules builds up inside the liver cells, but is usually thought as harmless. People usually does not have any symptoms. People may not even know this until they get an abnormal blood test result

Stage 2:

Stage 1 with focal or extensive portal fibrosis. It is also known as non-alcoholic steatohepatitis (NASH)

Only a small number of people with simple fatty liver later develop stage 2 of the condition, which is called as non-alcoholic steatohepatitis (NASH).

NASH is a more aggressive form of the disease. In this disease the liver has become inflamed. Inflammation is one of the part of the body's response

to injury. People with NASH may experience a very dull or aching pain in the top right side of their abdomen

Stage 3:

Bridging fibrosis .focal or extensive.

Some of the people with NASH develop fibrosis, here constant inflammation in the liver cells results in the formation of fibrous tissue around the liver cells and blood vessels.

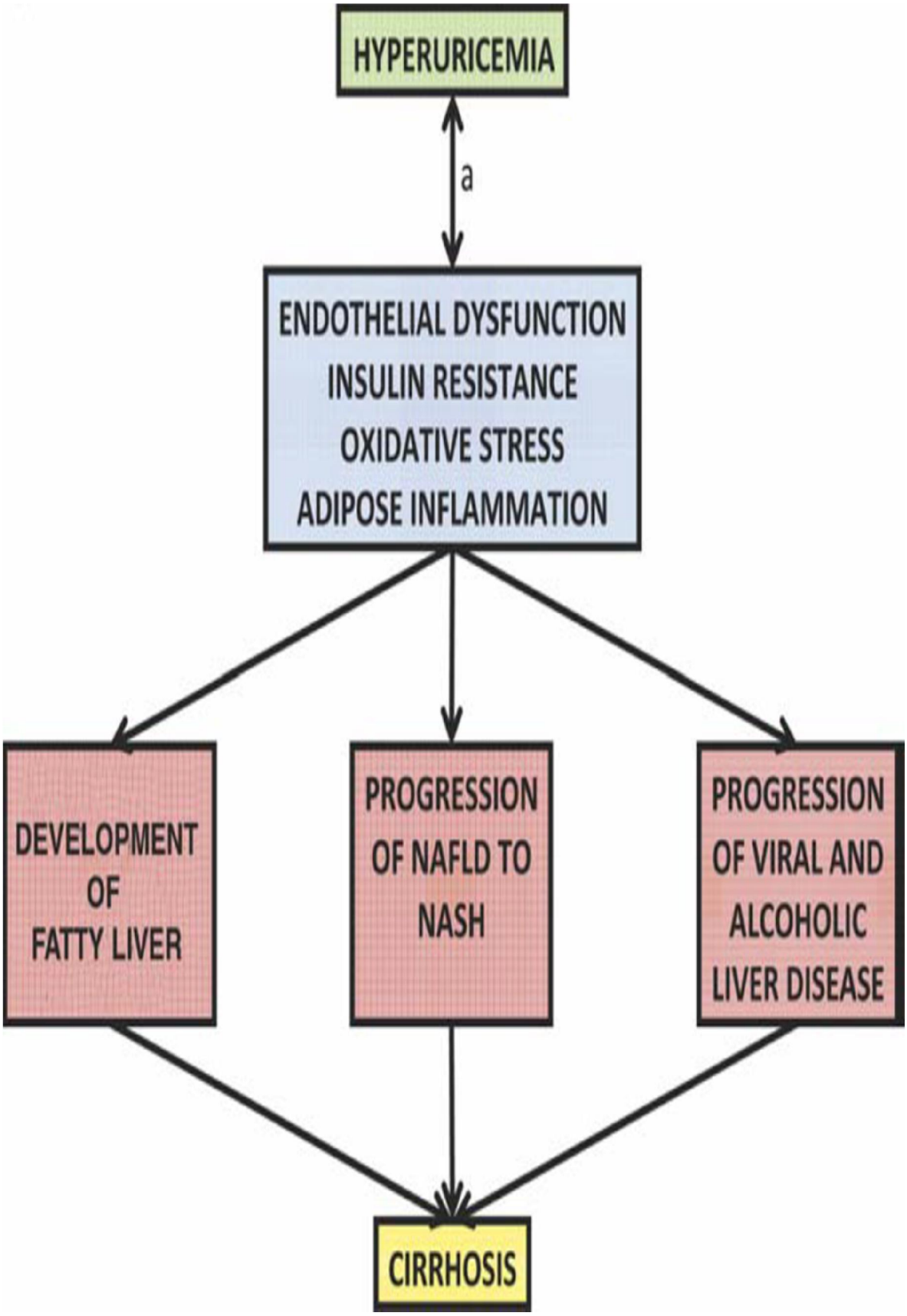
Stage 4:

Cirrhosis with or without peri sinusoidal residual fibrosis formation

This is the very severe stage. Here the liver cells has bands of scar tissue and clumping of liver cells. The liver reduces in size and becomes like a lump.

Cirrhosis usually occurs after 50-60 years of age following longer duration of inflammation of the liver associated with the early clinical stages of the disease.

But, this also can develop much earlier in some people. Patients with type 2 diabetes mellitus are at greatest risk of developing cirrhosis caused by NAFLD. Cirrhosis of liver causes permanent liver damage.


HYPERURICEMIA
a
ENDOTHELIAL DYSFUNCTION
INSULIN RESISTANCE
OXIDATIVE STRESS
ADIPOSE INFLAMMATION
DEVELOPMENT OF FATTY LIVER
PROGRESSION OF NAFLD TO NASH
PROGRESSION OF VIRAL AND ALCOHOLIC LIVER DISEASE
CIRRHOSIS

RISK FACTORS AND CONDITIONS ASSOCIATED WITH NAFLD

METABOLIC

Obesity

Type 2 diabetes mellitus

Hyperinsulinemia

Rapid weight loss including starvation and bypass surgeries

TPN

Lipodystrophy

MEDICATIONS

CARDIAC:

Amiodarone

Calcium channel blockers

Aspirin

STEROIDS:

Glucocorticoids

Synthetic estrogens

ANTIMICROBIALS:

Tetracycline

Antivirals such as zidovudine and didanosine

OTHERS:

Tamoxifen

Valproic acid

Methotrexate

Cocaine

OTHER CONDITIONS:

Inflammatory bowel disease

Small intestinal diverticulosis with bacterial overgrowth

HIV infection

Bacillus cereus infection

**EPIDERMIOLOGY OF MAJOR RISK FACTORS:**

Obesity-30 to 100 %

Type 2 diabetes mellitus-34 to 75 %

Hyperlipidemia-20 to81 %

## 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 internalized 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 complex 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 internalized 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 up regulated by

Insulin and experimental models of NAFLD.

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 which is stimulated by adrenaline, and inhibited by insulin

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.

Intra-hepatic fatty acids are cytotoxic and so are further metabolized 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.

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 oxidized 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 oxidized.

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

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

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

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.

**LIPOPROTEIN**

Definition:

Lipids synthesized in liver and intestine are insoluble. They are

Transported to many tissues in the body for metabolic functions through formation of macromolecular complexes called as Lipoproteins.

These are spherical shaped particles with the nonpolar lipid core containing Triglycerides and cholesterol esters. Peripheral polar lipid contains phospholipids and free cholesterol present near the surface.

They contain specific proteins which are called as Apo lipoproteins present on surface. They are attached none covalently through hydrogen bond and Vander Waals forces. Binding of lipids to protein is very loose

which allows ready exchange of lipids among the plasma lipoprotein and between cell membranes and lipoprotein

**Type of Lipoproteins:**

Lipoproteins are based on hydrated densities, separated by ultra-centrifugation. They are

- Chylomicrons
- Very low Density Lipoprotein
- Intermediate Density Lipoprotein
- High Density Lipoprotein
- Lipoprotein a.

Apo lipoproteins:

It is a protein component of lipoproteins. It is present in various proportions in all types of lipoprotein.

Apo A-I, Apo A-II, Apo A IV

Apo B-100, Apo B-48

ApoC-1, ApoC-II, ApoC-III

Apo-E,

Apo (a)

## Metabolism of Lipoprotein

The Pathways of lipoprotein metabolism are

1) Exogenous pathway

2) Endogenous pathway

3) Intracellular LDL receptor pathway

4) HDL Reverse – Cholesterol pathway

### 1. Exogenous Pathway (Chylomicron):

Lipoprotein is mostly of dietary origin. Dietary triglycerides and Cholesterol esters are arranged in secretary vesicles inside the Golgi apparatus to form nascent chylomicrons.

Chylomicrons is introduced into circulation through intestinal villi. Its lipid content is about 90% of Triglyceride and 2% of Apo B and Apo A. This Nascent chylomicron acquires Apo C and Apo E from high density lipoproteins to form Chylomicron.

Apo C-II present on the surface of chylomicron activates lipoprotein lipase, which is attached to luminal surface of endothelial cells of intestine. Lipoprotein lipase hydrolysis triglycerides to free fatty acids, which then taken up by the muscles for energy and adipose tissue for storage.

Apo A, some phospholipids and free cholesterol are transferred from chylomicron to high density lipoprotein.

Thus new chylomicron which is formed is called chylomicron-remnant, which contains TGL, Apo B-8 & Apo E. Presence of Apo B-48 and Apo E is recognized by a specific hepatic remnant receptor which is internalized by endocytosis.

Lysozymes hydrolyses chylomicron remnants to form bile acids. Chylomicron is incorporated into newly formed lipoprotein or stored as cholesteryl ester

2. Endogenous Pathway:

Lipoprotein is purely of hepatic origin, Triglycerides and Cholesterol can also be synthesized in liver. Endogenous Triglyceride and cholesterol are packaged in secretary vesicles in Golgi apparatus which is transported by exocytosis into extra cellular fluid and then into the circulation, in the form of Nascent very low density lipoproteins, containing 55% TGL and Apo B-100, Apo E and also small amount of Apo C on its surface.

Additional Apo E and Apo C are transferred from circulating high density lipoproteins to nascent VLDL forming very low density lipoproteins. Apo II present on surface of VLDL activates lipoproteins on endothelial

cells and also hydrolysis VLDL & TGL releasing free fatty acids and glycerol.

During hydrolysis Apo C is transferred back to high density lipoproteins. VLDL is converted to VLDL remnants & are taken up by liver and rest are converted to intermediate density lipoproteins. IDL has Apo E on surface, hence it binds to hepatic remnant receptor removing nearly 50% of IDL.

Some materials from intermediate density lipoproteins that is phospholipids, free cholesterol, and apolipoprotein are transferred to high density lipoproteins to form HDL-De nova. Cholesterol esters are transferred from high density lipoproteins to low density lipoproteins.

The net result of lipolysis and cholesterol esters exchange is replacement of triglyceride core of very low density lipoproteins with cholesterol esters. Further intermediate density lipoproteins undergoes lipolysis removing the remaining triglycerides and all Apo lipoproteins except B-100 to form low density lipoproteins.

3. LDL receptor Pathway:

There are specific receptors which are present in coated pits of plasma membrane, which recognize and bind to ApoB 100 of LDL. The particles are internalized in coated vesicle to form endosome, receptor dissociate from

low density lipoproteins and return to cell surface. Low density lipoproteins migrate to lysosome, ApoB 100 is degraded to small peptides and amino acids.

Cholesterol esters are hydrolyzed and free cholesterol is available for synthesis of cell membranes, steroid hormones and bile acids.

Increased supply of free cholesterol leads to:

1. Decreased rate of synthesis of endogenous cholesterol by inhibiting rate limiting enzyme HMG-COA reductase.

2. Increased formation of cholestryl esters catalysed by ACAT.

3. Inhibition of the Synthesis of new low density lipoprotein receptors by inhibition of transcription of receptor gene.

Low density lipoproteins is also taken up by extra hepatic tissues through scavenger receptors or non-receptor mediated pinocytosis. The non-receptor mediated uptake become important as plasma concentration increase as in the case of familial hypercholesterolemia.

Non receptor mediated uptake is not saturated or regulated. Scavenger receptor is also unregulated, found in macrophages and other cells. Macrophages engorge cholesteryl esters to form foam cells, considered the earliest component of atherosclerotic lesion.2/3 rd. of low density

lipoproteins is removed by low density lipoproteins receptors and remaining by scavenger cell system

**BODY MASS INDEX**

The most commonly used method for assessing obesity.

Body mass index (BMI) is defined as weight in kilograms divided by the square of height in metre (kg/m2)

$$BMI = \frac{\text{Weight (Kg)}}{(\text{Height in metres})^2}$$

OR

$$BMI = \frac{703 \times \text{Weight (lb)}}{(\text{Height in inches})^2}$$

According to the recommendations by the World Health Organization (2000),BMI of less than 18.50 kg/m2 denotes underweight, BMI of 18.50–24.99 kg/m2 normal weight, BMI of 25.00–29.99 kg/m2 overweight, and BMI of 30.00 kg/m2 obesity. In Asian and Pacific area populations, a specific BMI reflects a higher percentage of body fat compared to same BMI in Europeans.

BMI Prime

It is a simple change in the BMI measurement system. It is defined as the ratio of actual body mass index to the upper limit of BMI (currently defined at BMI 25). As defined above it is also defined as the ratio of the

body weight to its upper body weight limit, which is calculated at BMI 25. As it is a ratio of two separate body mass index values, the BMI Prime is defined as a dimensionless number without any associated unit. People with body mass index Prime lower than 0.74 are called as underweight, those people between 0.74 and 1.00 are called optimal weight and those people the level 1.00 or greater are called as overweight.

BMI Prime is more clinically useful because the individuals can tell, by what percentage they are deviated from their upper limit of weight. For instance, persons with the BMI of 34.00 have a BMI Prime of 34/25 = 1.36, and this is nearly 36% higher than his or her upper limit of body mass index.

In South East Asian populations and South Chinese populations the BMI Prime level should be calculated using an upper limit body mass index of 23 in the denominator instead of 25 which is commonly used. BMI Prime helps in easy comparison of populations in various countries and whose upper limit BMI values changes or differ

Categories

An important use of the body mass index is to assess, how the individual's body weight varies from the desirable or normal for his or her height and weight. The excess weight or reduced weight accounted for amount of fat in the body, even though other factors such as increased musculature also affects the BMI significantly. The WHO classifies the people if the BMI of

less than 18.5 as underweight, which indicates the person maybe having malnutrition or eating disorder, or some other health problems. If the BMI of a person is greater than 25 it is considered as overweight and BMI above 30 is considered as obese. These ranges of BMI values are valid and also as statistical categories

| BMI | Classification |
|---|---|
| < 18.5 | Underweight |
| 18.5 – 24.9 | Normal |
| 25 – 29.9 | Overweight |
| > 30.0 | Obesity |

**Waist circumference**

It is a method for detecting obesity and its related risks. It is widely accepted that central obesity is more detrimental than peripheral obesity, waist circumference is often a better predictor of diseases than BMI. The cut-off points for elevated waist circumference should be population and country specific.

The circumference of waist is calculated strictly at the level midway in between the lowest rib on both sides and the iliac crest of the hip. The waist

hip ratio is calculated by dividing the waist circumference by the hip circumference. But usually the waist circumference is measured at the level of smallest circumference of the natural waist in the body which is usually just above the level of belly button.

If the shape of the waist is convex than concave, for example in case of patients with pregnancy and obesity, the waist is measured at the vertical level which is one inch above the level of navel.

The measurement of size of a person's waist circumference usually indicates the development of abdominal obesity. Increased levels of abdominal fat is also an important risk factor for future development of heart disease and other obesity related diseases. The National Heart, Lung, and Blood Institute (NHLBI) classified that the risk of development of obesity related diseases is much high if the men have the waist circumference of more than 102 cms or 40 inches and women who have the waist circumference of more than 88 cm or 35 inches

| Waist Girth and Health Risk | | |
|---|---|---|
| | Men | Women |
| Normal | 78-94cm | 64-80cm |
| Overweight (Elevated Risk) | 94-102cm | 80-88cm |
| Obese (High Risk) | >102cm | >88cm |

**Laboratory tests**

Advanced liver disease produce abnormalities in several laboratory markers. The measurements of serum liver enzymes serve as important diagnostic information. Serum uric acid is not a liver marker per se, but is included because of its role as a possible indicator of oxidative stress.

1. Gamma-Glutamyltransferase (GGT)

Serum Gamma-glutamyltransferase (GGT) is an enzyme derived from the liver, the changes in its activity used to monitor excessive alcohol consumption for several decades.

In fact, GGT has been the most commonly used laboratory marker of heavy drinking. it may also elevated due to diabetes mellitus, obesity, pancreatitis, hyperlipidemia, cardiac insufficiency, severe trauma, nephrotic

syndrome, renal rejection, and medication, and in patients with other than alcoholic forms of liver diseases. Non-ethanol related liver changes usually do not show profound changes in their GGT in the short-term.

Documentation of decreased activity can be helpful in the differential diagnosis in pointing toward alcohol etiology, markedly increased GGT activities are usually considered to reflect tissue damage when they associated with abnormalities in other liver enzymes.

Mild elevations of GGT relate to its biological function to maintain the intracellular levels of glutathione and also to metabolize glutathione conjugates. Glutathione is an important antioxidant, ant its removal causes loss of viability.

In general oxidative stress is associated with diseases of the modern life which includes cancer, neurodegenerative diseases, rheumatoid arthritis, atherosclerosis, NAFLD, obesity, diabetes, the metabolic syndrome, and others.

2. Aminotransferases (ALT, AST)

Aminotransferases are measured primarily to assess the condition of the liver. Serum alanine aminotransferase (ALT) originates specifically from the hepatocytes, whereas aspartate aminotransferase (AST) can also arise from heart and skeletal muscle tissue.

In an asymptomatic patient, the activities of serum aminotransferases may be increased due to alcohol abuse, chronic hepatitis B ,hepatitis C, Medication , steatosis and NASH, hemochromatosis, autoimmune hepatitis, Wilson's disease (<40 years), alpha1-antitrypsin deficiency, genetic errors in muscle metabolism, celiac sprue acquired muscle diseases, and strenuous exercise.

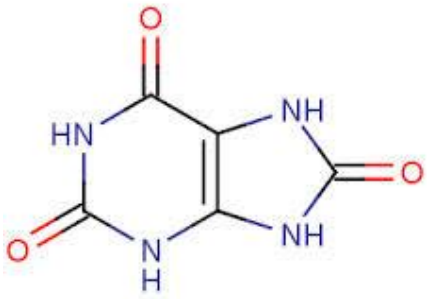
Aminotransferases also seem to associate with general health so that ALT appears to have a much stronger association with BMI than with alcohol consumption. ALT associates mainly with the hepatic fat content, and thus with NAFLD which, as a component of the metabolic syndrome, is highly related to the development of type 2 diabetes.

Elevated serum ALT in NAFLD may be a consequence of leakage from the damaged hepatocytes or due to increased gluconeogenesis in the absence of insulin.

3. ULTRASONAGRAM

It is a noninvasive method of investigation. Abdominal scan in case of liver disease shows various information regarding size and shape of the liver, echogenicity of the liver, fluid collections inside the body cavity, portal vein size and also information's regarding other abdominal organs

4. SERUM URIC ACID




Background

Uric acid is the end and final product of metabolism of purines in human. Even though the uric acid was first found nearly more than 200 years ago, some of the clinical aspects of hyperuricemia are not yet clearly understood.

For so many years increased uric acid levels has been identified with or thought as same as the disease gout. But now increased uric acid is one of the risk factor for numerous metabolic and also some abnormalities of hemodynamic system.

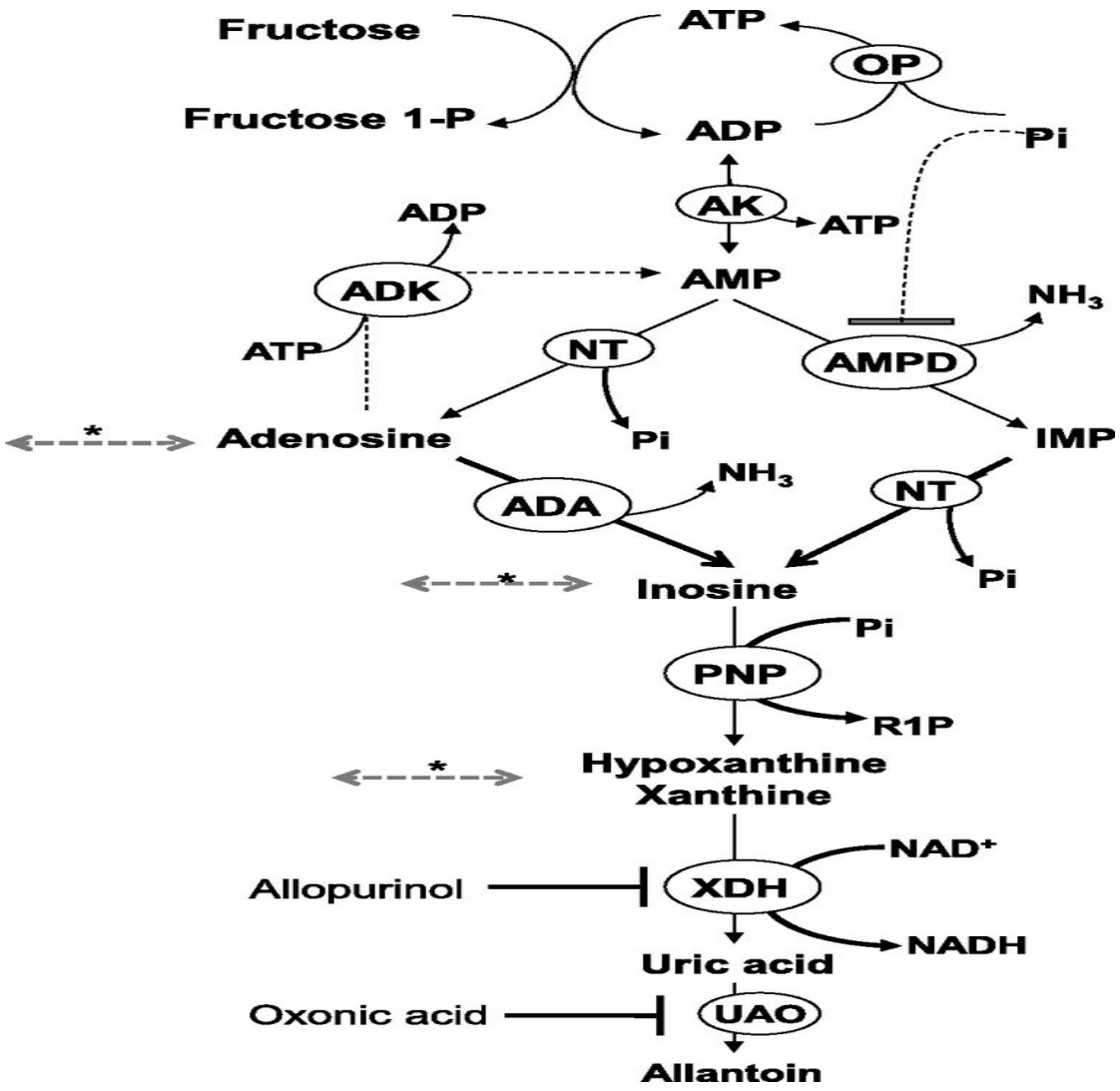
Allantoin, which is end product of purine metabolism is seen in lower animals is very much soluble but uric acid is a poorly soluble end product seen in humans.

Human beings have an increased levels of uric acid, due to the deficiency of the hepatic enzyme known as uricase and also due to a lower fractional excretion of uric acid by kidneys.

About 2/3 of total urate in humans is produced by the body is by endogenous means and the balance one third urate is due to the intake of dietary purines. Nearly 70% of the urate produced in body of humans is excreted daily mainly by the kidneys and the rest is removed by the human intestines.

However in cases of renal failure in humans, the intestinal excretion of urate excretion increases. The uric acid levels in the blood are the indications of the function of the balance between the purines breakdown and also the rate of uric acid elimination from the body.

So alterations in this balance which is increased intake and decreased elimination may theoretically contribute for the development of hyperuricemia ,but Clinically there is only the defective elimination accounts in most of the cases of hyperuricemia.




Patho physiology

Saturated Uric acid in the blood is about 6.4-6.8 mg/dL and in standard conditions, the upper limit of solubility is about 7 mg/dL. Urate in humans is freely filtered by the kidneys. It is reabsorbed in the glomerulus, again secreted and then again reabsorbed in the proximal convoluted tubule in the

kidneys. Cloning of the certain types of urate transporters recently gained importance in the understanding of mechanisms by which the urate in the humans are handled both by the kidneys and the small intestines.

A urate anion exchanger known as URAT1 has been found in the brush border membranes and this is well blocked by the drug an angiotensin II receptor blocker, called losartan.

Another transporter a human organic anion transporter (hOAT1) also found to be blocked by both the uricosuric and the anti uricosuric drugs

Transporter UAT also found to increase the urate efflux out of the human cells. These cell transporter may also account for the reabsorption and secretion by the kidneys

However the secretion of urate correlated well with the serum levels of urate because even a very minimal increase in the serum concentration of urate causes a marked increase in urate excretion by the kidneys. So increased uric acid levels may occur because of decreased excretion or increased production or may be a combination of two

Reduced excretion of urate is the most common cause of hyperuricemia in humans. Alteration in uric acid excretion may results in decreased glomerular filtration and decreased tubular secretion or there may be an enhanced tubular reabsorption.

But decreased filtration of urate usually does not cause primary hyperuricemia, but it can contribute to the increased uric acid levels in renal failure.

Decreased tubular secretion of urate seen in conditions with acidosis like diabetic ketoacidosis, salicylate or ethanol intoxication and starvation ketosis.

The organic acids which can accumulated in these above conditions compete with the urate for tubular secretion. Increased reabsorption of uric acid distal to the site of secretion is the main mechanism to be responsible for the increased uric acid levels observed in diuretic therapy and in patients with diabetes insipidus.

Increased production of urate accounts for only a minimal number of patients presenting with increased uric acid levels.

The causes for increased serum uric acid levels in overproducers may be due to exogenous diet rich in purines or maybe endogenous due to increased breakdown of purine nucleotide.

Only a very small percentage of urate overproducers have defects in their enzymatic levels which accounts for their overproduction of uric acid. This includes a complete absence of the enzyme hypoxanthine guanine phosphor ribosyl transferase (HGPRT) as seen in Lesch Nyhan syndrome or

partial deficiency of HGPRT as in Kelley-Seegmiller syndrome and increased production of 5 phospho alpha-d-ribosyl pyrophosphate (PRPP).

Increased degradation of purines may result from increased cell proliferation and turnover as in blast crisis of leukemia or from cell death as is rhabdomyolysis or cytotoxic drug therapy. Glycogenoses type III, type IV, and type VII can also result in increased uric acid levels due to increased degradation of skeletal muscle ATP.

Combined mechanisms of reduced excretion and increased production of urate can also cause increased uric acid levels. Most common cause of this group is increased alcohol intake, which then results in increased hepatic breakdown of ATP and the production of organic acids which will compete with the urate for tubular secretion.

Enzymatic defects such as glycogenoses type I and aldolase B deficiency are some other causes of increased levels of uric acid that result from a combination of increased production and defective excretion.

Now new findings showed that urate crystals can also be incorporated in an intracellular pattern recognition receptor known as macromolecular inflammasome complex. NALP3 (cryopyrin),NALP3 inflammasome may also result in the production of interleukin 1 beta which, in turn starts an inflammatory response Inhibition of this pathway also has a potential to

targeted for increased uric acid levels induced crystal arthritis and development of new drugs

Frequency

A study about uric acid in japan ascertain 10 year database trends in the prevalence of hyperuricemia confirmed that prevalence of increased uric acid in japan associated with many diseases

When this data is analyzed and stratified by age, the prevalence of uric acid levels increased among people older than 65 years in both male and female. In people younger than 65 years of age men had a higher prevalence of 4 times than that of women in that age group. People who are older than 65 years the gender gap is narrowed and the female-to-male ratio of 1:3, with gout or with hyperuricemia.

Race

There is an increased prevalence of hyperuricemia seen in indigenous races of humans who are living in the Pacific region, which is appears to be associated with a reduced fractional excretion of uric acid in them. Africo American patients develop increased uric acid levels more commonly than the white persons.

Sex

Men are far more commonly affected by Hyperuricemia than Women. In gouty arthritis only about 5% of patients are female even though they have increased uric acid levels. Increased uric acid levels in women population after the menopause.

Age

The upper limit of the reference levels of uric acid for children is 5 mg/dl. or 0.30 mmol/L. The upper limit of the reference values of uric acid for men is 7 mg/dL or 0.42 mmol/L and for women is about 6 mg/dL or 0.36 mmol/L. As the age advances there is a tendency to develop hyperuricemia in both sex. The normal serum uric acid level is lower in children compared to adults.

Total body content in average adult is 1.2 g

Plasma uric acid is 3.5 – 7mg/dl in males and. 2.7 – 6.5 mg/dl in females

Average Adult excretes 400 – 600 mg in 24 hrs urine

On low purine diet 275 – 600 mg is excreted in 24 hrs urine.

On high purine diet up to 1gm in 24 hrs urine.

In Gout increase to 18000 – 30000 mg (total content)

**Sources of uric acid**

People may present with increased uric acid levels due to hereditary reasons. Diet may also act as factor for high uric acid. Increased levels of purines are seen in many animal food products, especially in the internal organs like intestine.

High purine resources includes sweetbreads, anchovy sauce, brains, beef kidneys, liver, sardines, extracts of meat like Oxo, Bovril, mackerel, scallops, gravy and game meats, beef, pork, poultry, fish ,seafood, asparagus, cauliflower, green peas, lentils, spinach, mushrooms, peas which are dried, oatmeal beans, wheat bran and wheat germ.

Moderate food intake of purine rich food is not usually associated with an increased risk of development of gout. Serum uric acid levels are also increased due to increased fructose intake, reduced excretion by the kidneys, and increased intake of dietary purine.

Fructose which are found in processed foods and soda beverages and also in the form of corn syrup also has increased risk.

Laboratory test

Uric acid by phosphotungstic acid method

Method of caraway.

Principle:

The procedure is based on oxidation of uric acid by phosphotungstic acid

Reagent in alkaline medium. Phosphotungstic acid itself gets reduced to tungsten blue. Sodium bi carbonate is used as alkali. The amount of tungsten blue formed is estimated at wavelength from (690-710nm) 660nm

Reagents

1) Sodium tungstate 10% - 100 gm. of sodium tungstate per litre of water.

2) 2/3 N Sulphuric acid – 18.8 ml of concentrated sulphuric acid per litre

Of water.

3) Tungstic acid has 50ml of 10% tungstate + 50 ml of 2/3 Sulphuric acid ($H_2SO_4$) then Add drop of phosphoric acid, and mix it in 800ml water then Preserved in bottles which are brown colour.

Phosphotungstic acid is 50g of sodium tungstate in about 400ml of

water then Add 40ml of 85% phosphoric acid and reflux it gently for 2hr and

Cool them and then transfer to 500ml flask and make it up to mark with water then the concentrated phosphotungstic acid is diluted to dilute phosphotungstic acid 1 to

10 for use and should be Kept in brown bottle.

5) Sodium carbonate 10% - 100gm of sodium carbonate in 1000ml of D/W

6) Standard Solution: Weigh out 100mg of uric acid in a small beaker. 60 mg of lithium carbonate is dissolved in 15-20 ml of D/W in a test tube then heat the test tube to about 600°C and pour on to uric acid Solution. Stir until dissolved, then heated further.

When dissolved, transfer with washing to 100ml flask. Add 2ml of 40% formalin. Then slowly with shaking, add 1ml of 50% acetic acid make up to mark with water and mix. Stored in well stoppered bottle away from light.

7) Working standard: Dilute 2ml of stock standard to 200ml of D/W

Procedure Deproteinisation: Add while shaking 5.4ml of dilute tungstic acid to 0.6 ml serum and centrifuge. Out of this take 3ml of supernatant and add 0.6 ml of sodium carbonate and 0.6ml of phosphotungistic acid .Mix and take OD after 30min at 700nm or red filler.

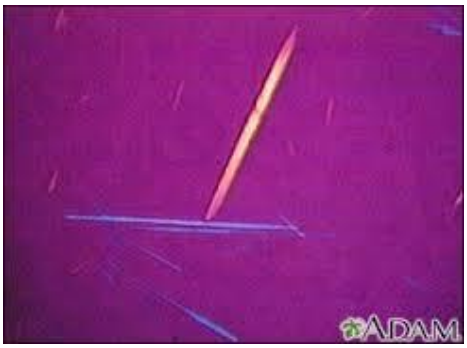
Similarly take 3ml of Standard .Add 0.6ml of Sodium carbonate & 0.6ml of phosphotungstic acid. Mix & take OD after 30min at 700mm. Concentration of Standard is 0.03

Volume of test is 0.3

Calculation: Uric acid in 100ml serum OD of test conc. of STD

---------- x ---------- x 100 = ---- ml /dl

OD of STD volume of test




Anti-oxidant capacity

Uric acid is thought to be a marker of increased oxidative stress. Uric acid has a good therapeutic role as an antioxidant, like other reducing substances which has antioxidant properties such as ascorbate. Uric acid also acts as a peroxidant, most commonly at increased or elevated levels in serum.

It is not very clear that whether increased levels of uric acid in diseases associated with oxidative stress like stroke, atherosclerosis and cerebrovascular accident are a protective response or a primary cause for these diseases.

So some of the researchers thought that hyper uricemia induces oxidative stress which is a cause of metabolic syndrome. At the other side increased plasma uric acid levels corresponds with longevity in primates and other animals. This may be due to its function as antioxidant

Mortality and Morbidity

In patients with hypertension and hyperuricemia have increased morbidity and significant association with each other. Increased serum uric acid levels also associated with increased in the mortality patients who are all women and aged persons. Because for this increased mortality is unknown, but hyperuricemia maybe a marker for comorbid risk factors in diseases rather than a causative factor.

## URIC ACID AND VARIOUS DISEASES

High serum uric acid levels and low serum uric acid levels associated with many human illness and disease state. An abnormally increased serum uric acid level has been associated with the development of gout, hypertension, renal disease and cardiovascular disease in humans.

Hypouricemia associated with the development of CNS diseases like Alzheimer's disease, Multiple sclerosis, Parkinson's disease, and optic neuritis

Alternatively increasing serum uric acid has been used for the treatment of neurodegenerative diseases of brain for example multiple sclerosis and for

the management of both stroke and spinal cord damage or injury. Use of hyperuricemia in management of these disease is due to its neuroprotective effects and properties

**Uric Acid Balance**

In extra cellular fluid, uric acid which is a weak acid distributed in the form of sodium urate. The amount of urate seen in the blood depends on the intake of purines through diet, amount of urate excretion and biosynthesis of urate.

Serum uric acid levels are regulated by a four components renal transport system which involves glomerular filtration, glomerular secretion, reabsorption and post secretory reabsorption.

There are many kidney urate transporters system are involved in the regulation of serum and plasma urate levels in humans. They include urate transporter 1 also called as URAT1, this is also responsible for the reabsorption of urate in the kidneys. There are many other number of organic ion transporters (OAT) in urate transport system, such as organic ion transporters OAT1 and OAT3 . Also ATP-dependent urate export transporter that is MRP4 also involved in the secretion of urate.

Nearly 90% of the filtered urate in human kidneys are reabsorbed, because of the involvement URAT 1 in urate reabsorption. URAT1 is thought as a very critical in the regulation of plasma urate levels in kidneys.

**Hyperuricemia and Hypertension**

Hyperuricemia has strong association in predicting the development of hypertension in the general population, the elevated levels of serum uric acid may be due to the decrease in renal blood flow which develops in the early stages of hypertension.

A reduced blood flow in renal vasculature alters the medullary and cortical circulation balance, which then resulting in a decreased secretion of urate by the kidneys.

Hypertension can also lead to microvascular disease resulting in local tissue ischemia .This tissue ischemia leads to an increase in the production of uric acid resulting in an increased serum uric acid level. These mechanisms in kidney clearly shows that the increase in the plasma levels of uric acid may be a consequence of hypertension**.**

**Hyperuricemia in Cardiovascular Disease**

Hyperuricemia is a major risk factor for the development of cardiovascular diseases like myocardial infarction, and stroke. Elevated

serum uric acid levels are also act as an independent risk factor for increased cardiovascular mortality.

Increased serum uric acid levels associated with increased cardiovascular disease, this may be due to its antioxidant property. Increased levels of uric acid also contribute to the increased number of cardiovascular disease due to its negative effect on the endothelium in the vessels.

Levels if Uric acid concentrations sometimes increase due to its attempt to block peroxidation of lipids and other related reactions. This also clearly shows that increased uric acid levels are a consequence of cardiac disease.

There is also some other evidences that shows serum uric acid can possibly increase rather than prevent oxygenation of cholesterol, low density lipoprotein and Peroxidation of lipids. This leads to an increase in the adhesiveness of platelets to the vessels which then results in formation of thrombus. This thrombus formation then contribute to the development of atherosclerosis and also increases the future development of cardiovascular disease.

This increased serum uric acid levels also stimulates the release of free radicals, which are thought to be involved in the expression of adhesion molecules both by the inflammatory cells and inflammatory cell activation. Adherence of this free radicles to the damaged endothelium causes one of

the component of Virchow's triad. This later results injury to the endothelial cells and increasing the risk of development of cardiovascular disease.

**Uric Acid and Neuroprotection**

Uric acid has up to 60 % of scavenging the free radicals in the human blood due to its natural anti-oxidant property. Uric acid can scavenge various free radicals like superoxide, the hydroxyl radical, and singlet oxygen. Uric acid helps in the removal of superoxide by acting against the destruction of superoxide dismutase which is an enzyme.

Superoxidase dismutase enzyme is very important for removing the superoxide from the cells of the humans. Removal of superoxide by this enzyme helps in prevention of its reaction with nitric oxide by blocking the production of peroxynitrite.

Uric acid is very effective in preventing peroxynitrite, which are part of proteins in the cell. By this way they prevent the inactivation of cellular enzymes and the cytoskeleton modification.

Uric acid acts in astroglia which present in the central nervous system.in this cells uric acid up regulates the protein levels of EAAT-1 .EAAT-1, which is a glutamate transporter protects the neurons in the spinal

cord from toxicity induced by glutamate. Uric acid protects the cells through a direct, astroglia mediated mechanism.

**Hyperuricemia in gout**

Gout is a type of crystal deposition disease. It is the most common form of arthritis involving joints due to errors in metabolism of purine. Monosodium urate crystals which are formed due to the error in metabolism are deposited in the joints and tissues around the joints

Gout are known in very ancient period and one of the oldest known disease. Gout clinically cause inflammation which are painful around the joints of lower or upper extremities. It sometimes affects more than one joints. Most commonly it affects the lower extremity. Nodules formed by gout which are deposited in soft tissues are called as tophi.

Acute attack of gout causes painful joints which lasts for a short period and causes the patient a temporary disablement. This acute attacks of gout later predispose to further attacks of gout in future.

The main cause for development of gout is increased levels of uric acid in blood which are metabolic by products of purines. This increased levels of uric acid also called as hyperuricemia. This increased levels of uric acid is calculated to affect approximately 20 % of population.

# MATERIALS AND METHODS

## STUDY DESIGN

This is a prospective study conducted on a sample south Indian population admitted in department of medicine and department of gastroenterology during the period of 2013 and 2014. The study includes a standardized questionnaire and examination based on this patients were included in this study. A total number of 100 patients who are all diagnosed to have fatty liver and cirrhosis are included in this study. Patients with prior history of alcoholic liver disease, chronic kidney disease, arthritis, cardiovascular disease and diabetes mellitus, hypothyroidism are excluded. The total number of patients included in this study was 100 out of which 75 are males and 25 are females

## INCLUSION CRITERIA

Age of the patients between 30 years to 60 years without the prior history of alcoholism, diabetes mellitus, kidney disease, hypothyroidism, drug intake and cardiac disease

## EXCLUSION CRITERIA

1. Age less than 30 years and more than 60 years

2. Gout

3. Chronic alcoholics

4. Known case of alcoholic liver disease

5. Chronic kidney disease

6. Hypothyroidism

7. Drug intake

8. Diabetes mellitus

9. Cardiac disease

10. Obesity

## METHODS

A detailed history was elicited from the patient regarding their present complaints, associated symptoms, alcohol intake, smoking, previous history of hypertension, diabetes mellitus, arthritis, hypothyroidism, any cardiac illnesses and chronic drug intake.

On admission routine blood investigations like blood sugar, urea, serum creatinine, liver function test, thyroid profile, lipid profile, ultra sonogram and serum uric acid levels were estimated. Waist circumference in males and females measured. Diabetes was defined as fasting blood sugar >126 mg % and post prandial blood sugar >200 mgs%. Body mass index was calculated as weight in kg/ height in m2. Serum uric acid levels also sent for analysis on the day of admission. The reagent for serum uric acid is uricase and for blood glucose trider method is used.

## STATISTICAL ANALYSIS

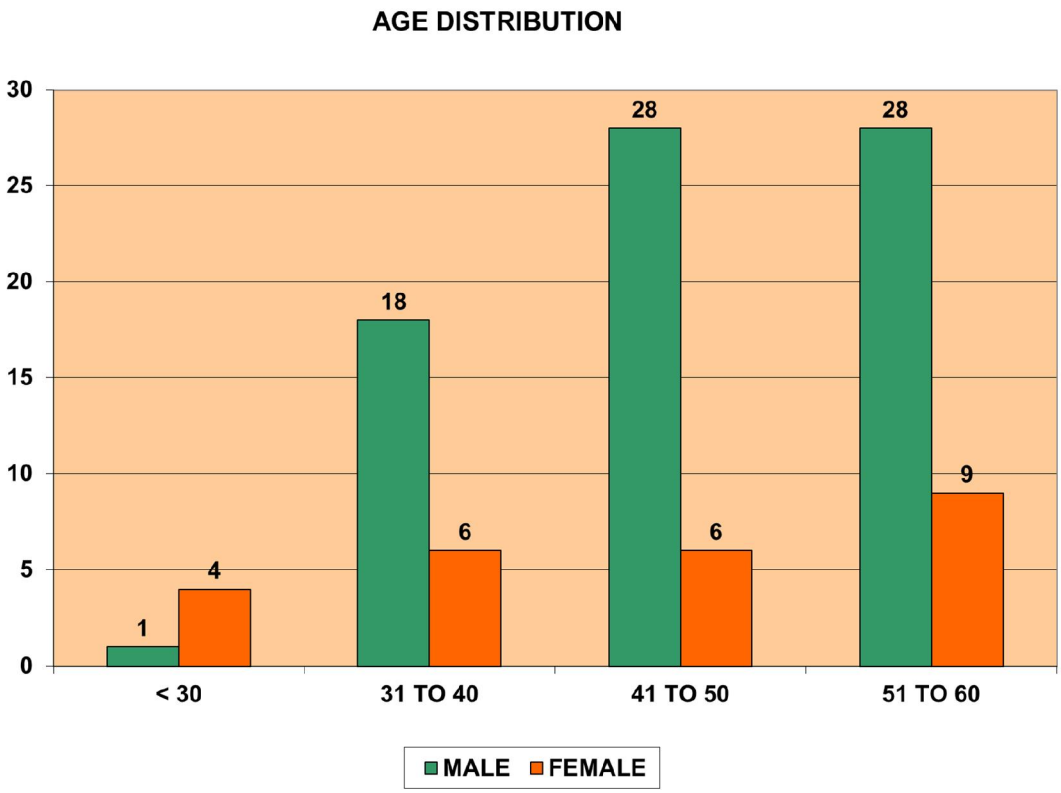
Data analysis was done and the subjects were divided in to two groups. One group with ultrasonagram findings of fatty liver and another group with the findings of cirrhosis of liver. Serum uric acid levels in both the groups are analysed with age and sex

Using the SPSS 20 and sigma stat 3.5 version software, means, standard deviations, range, frequencies, percentages, chi-square and 'p' values were calculated. One way ANONA and student's t test for data and chi square test for consolidation of tables used. A 'p' value of $< 0.05$ was taken as significant relationship.

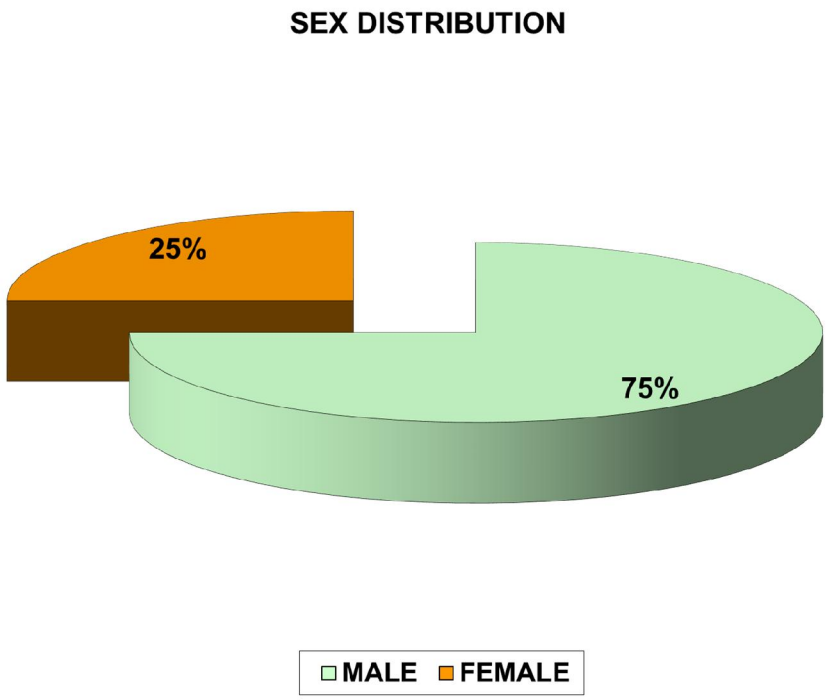
## RESULTS AND OBSERVATIONS

The study population has 100 patient in the age group of 30 years to 60 years. The mean age of total population is 46.81. The mean age for male is 47.52. The mean age for female is 44.68

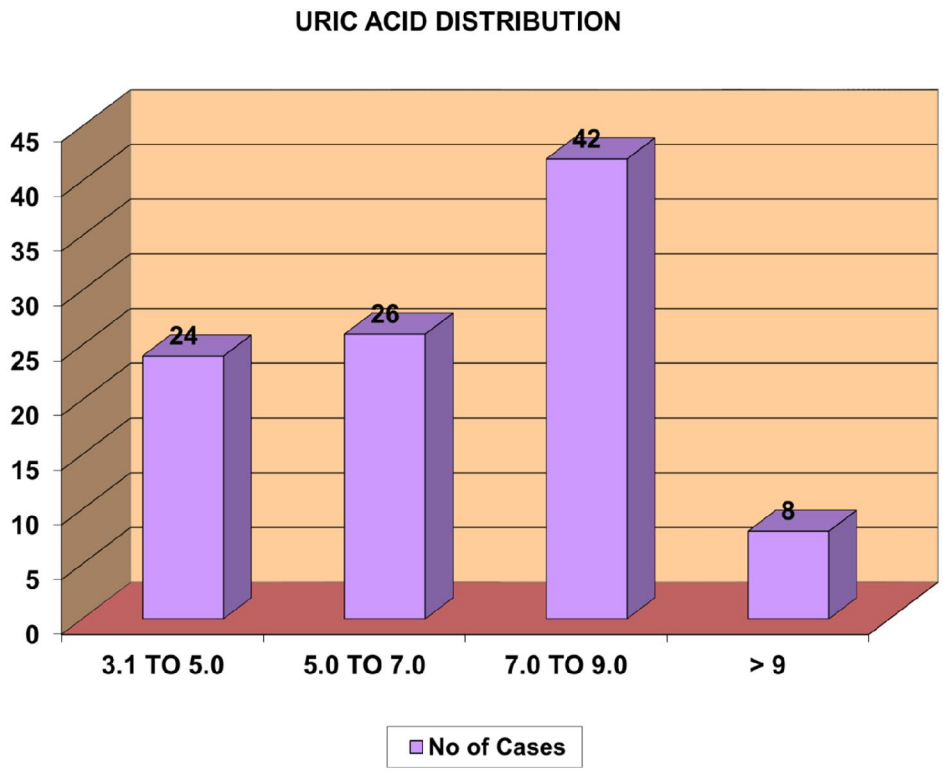
| AGE DISTRIBUTION IN STUDY POPULATION | | | | |
|---|---|---|---|---|
| AGE | MALE | FEMALE | Total | |
| < 30 | 1 | 4 | 5 | |
| 31 TO 40 | 18 | 6 | 24 | |
| 41 TO 50 | 28 | 6 | 34 | |
| 51 TO 60 | 28 | 9 | 37 | |
| TOTAL | 75 | 25 | 100 | |




The mean age of the total population was 46.81 years. The mean age of male was 47.52years and the mean age of female was 44.68. The mean age for male is higher than female

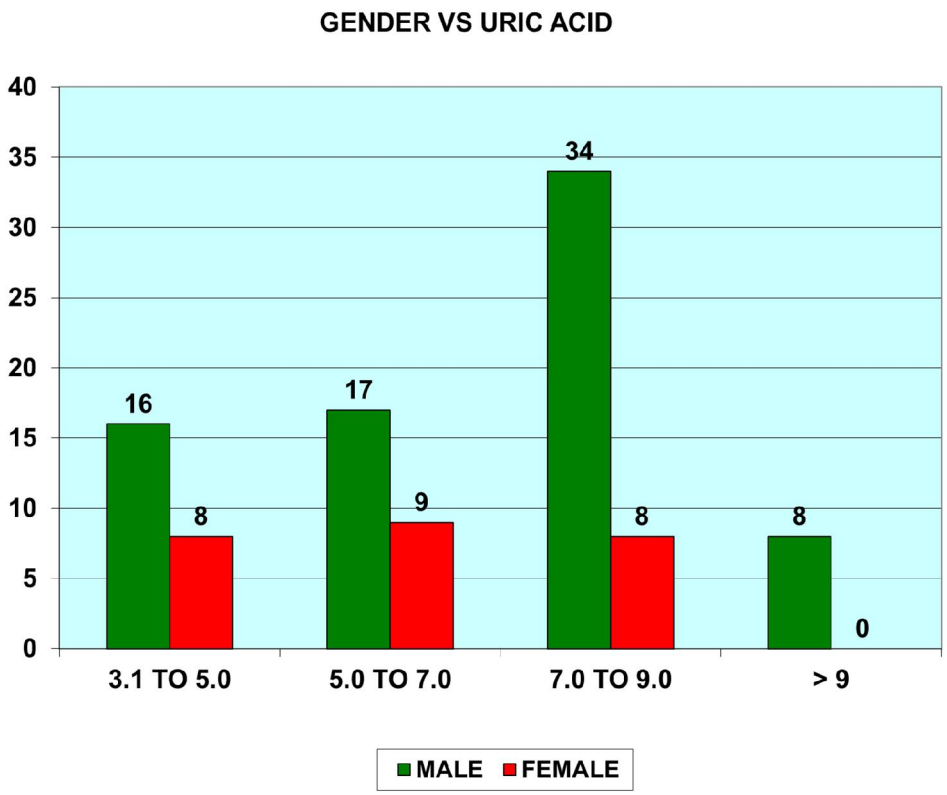



The studied population had 75% of males and 25% of females



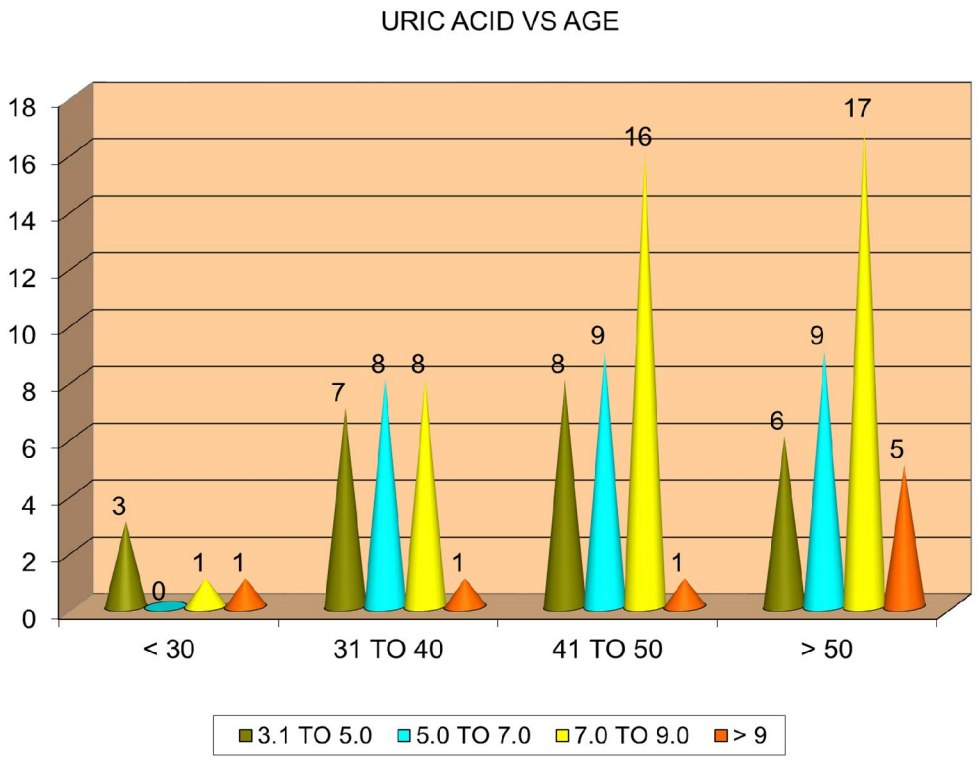

The studied population showed among the 100 patients 42 persons had hyperuricemia in the average of 7 to 9. The mean uric acid level is 6.73

| URIC ACID | | |
|---|---|---|
| | | |
| URIC ACID | No of Cases | |
| 3.1 TO 5.0 | 24 | |
| 5.0 TO 7.0 | 26 | |
| 7.0 TO 9.0 | 42 | |
| > 9 | 8 | |
| TOTAL | 100 | |




Mean uric level in the studied population was 6.73. Men had relatively higher uric acid levels when compared to women. P value is 0.002 which is significant in this study. Mean uric acid level in male was 6.93 and mean uric acid in female was 6.11.

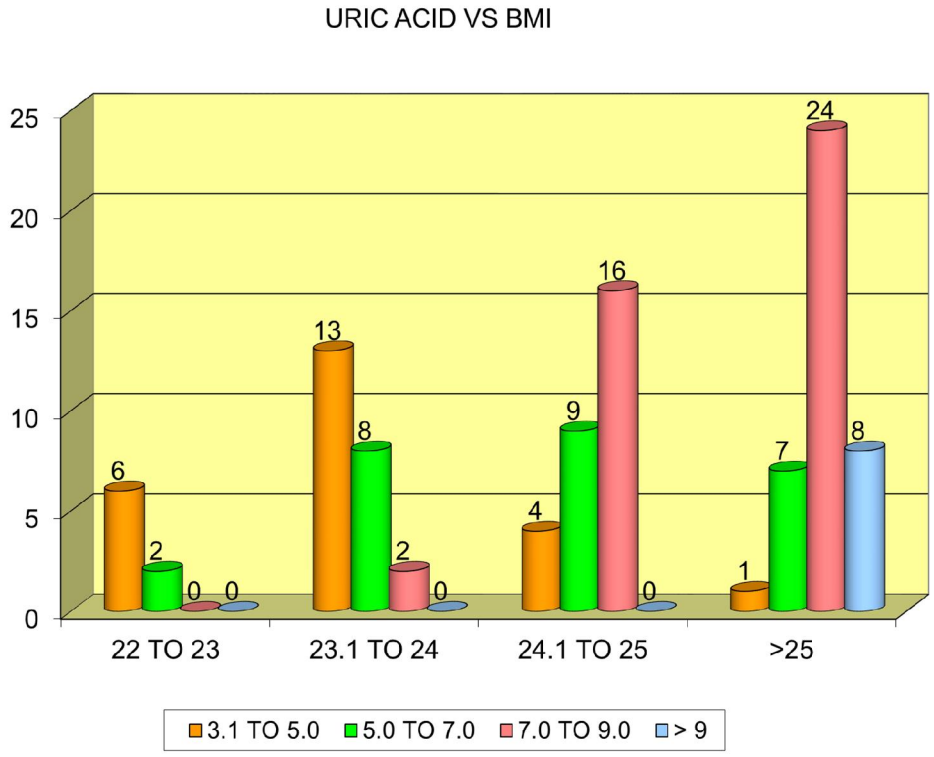
| URIC DISTRIBUTION IN MALE AND FEMALE | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| URIC ACID | MALE | FEMALE | TOTAL | | . |
| 3.1 TO 5.0 | 16 | 8 | 24 | | |
| 5.0 TO 7.0 | 17 | 9 | 26 | | |
| 7.0 TO 9.0 | 34 | 8 | 42 | | 0.002 Significant |
| | | | | | |
| > 9 | 8 | 0 | 8 | | |
| TOTAL | 75 | 25 | | | |




In this studied population patients in the older age group had higher uric acid levels compared to the younger patients. But the P value is o.792 which showed no significance

| URIC ACID AND AGE | | | | | |
|---|---|---|---|---|---|
| | | | | | |
| URIC ACID | < 30 | 31 TO 40 | 41 TO 50 | > 50 | |
| 3.1 TO 5.0 | 3 | 7 | 8 | 6 | |
| 5.0 TO 7.0 | 0 | 8 | 9 | 9 | |
| 7.0 TO 9.0 | 1 | 8 | 16 | 17 | 0.792 Not significant |
| > 9 | 1 | 1 | 1 | 5 | |

| | | | | | |
|---|---|---|---|---|---|
| TOTAL | 5 | 24 | 34 | 37 | |



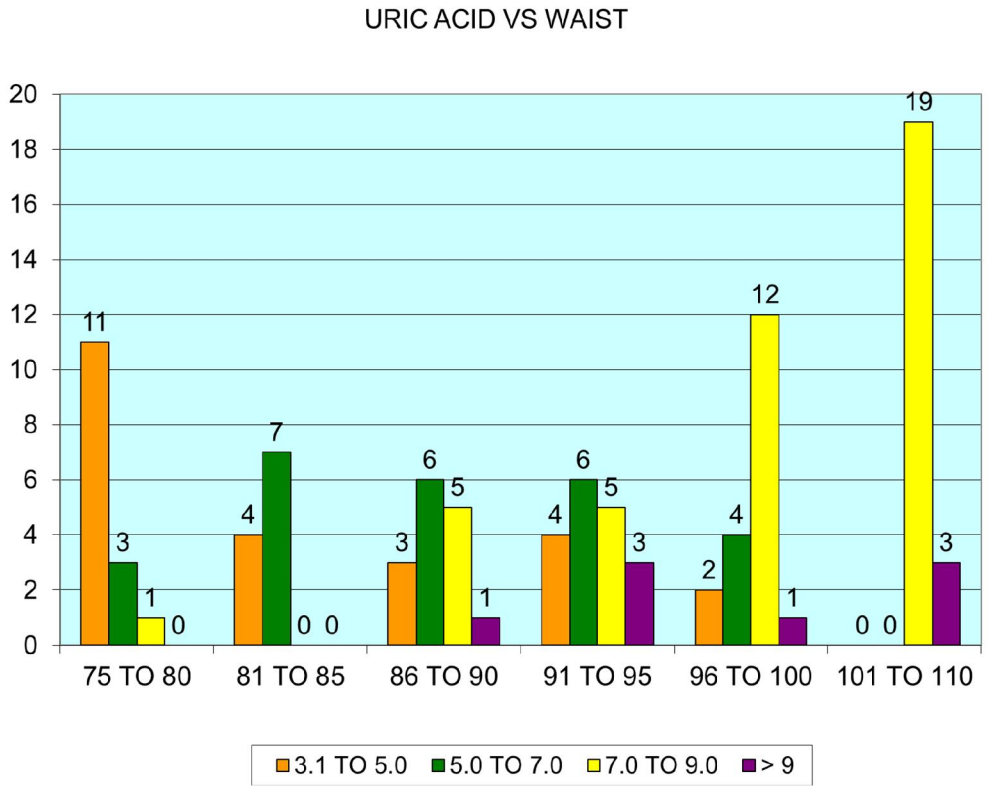

In the studied population BMI, hyperuricemia associated with high BMI which is significant. P value is 0.009

Uric acid and BMI

| URIC ACID | 22 TO 23 | 23.1 TO 24 | 24.1 TO 25 | >25 |
|---|---|---|---|---|
| 3.1 TO 5.0 | 6 | 13 | 4 | 1 |
| 5.0 TO 7.0 | 2 | 8 | 9 | 7 |

| | | | | |
|---|---|---|---|---|
| 7.0 TO 9.0 | 0 | 2 | 16 | 24 |
| > 9 | 0 | 0 | 0 | 8 |
| TOTAL | 8 | 23 | | |

0.009 Significant



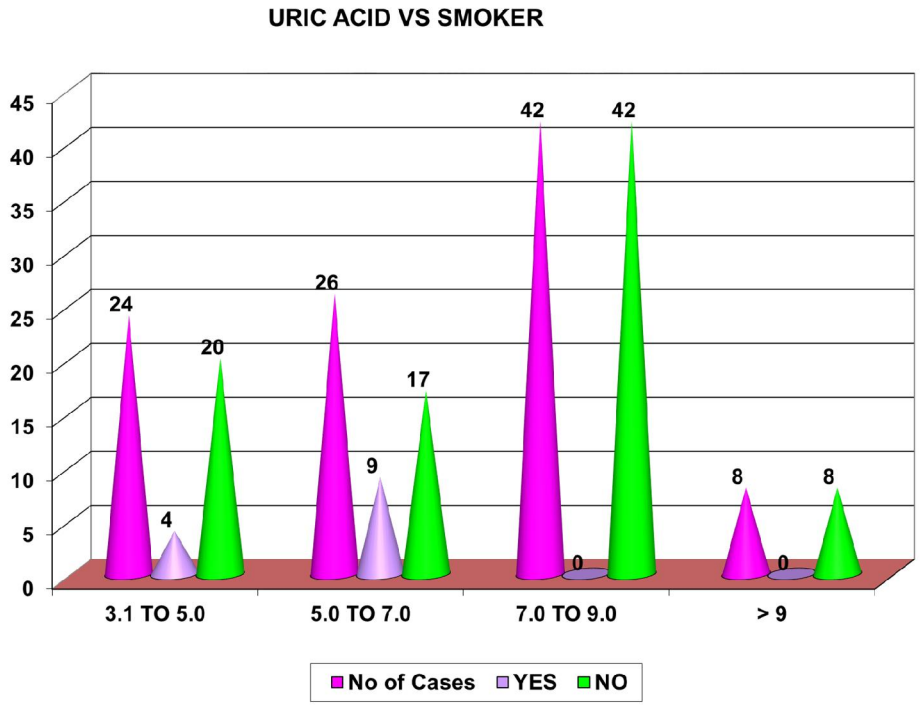

In this studied population patient with hyperuricemia associated with increased waist circumference which is significant. P value is 0.012

URIC ACID AND WAIST

| URIC ACID | 75 TO 80 | 81 TO 85 | 86 TO 90 | 91 TO 95 | 96 TO 100 | 101 TO 110 |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| 3.1 TO 5.0 | 11 | 4 | 3 | 4 | 2 | 0 |
| 5.0 TO 7.0 | 3 | 7 | 6 | 6 | 4 | 0 |
| 7.0 TO 9.0 | 1 | 0 | 5 | 5 | 12 | 19 |
| > 9 | 0 | 0 | 1 | 3 | 1 | 3 |
| TOTAL | 100 | | | | | |

0.012 Significant

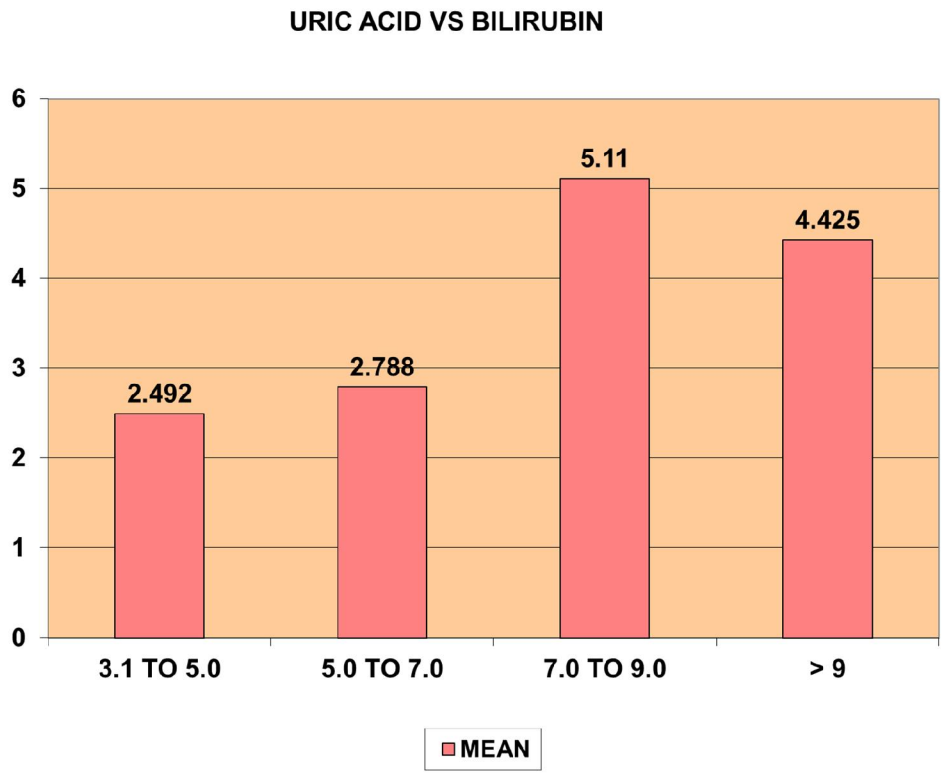



In this studied population smoking does not correlated with hyperuricemia

SMOKER

| URIC ACID | No of Cases | YES | NO |
|---|---|---|---|
| 3.1 TO 5.0 | 24 | 4 | 20 |
| 5.0 TO 7.0 | 26 | 9 | 17 |

| | | | |
|---|---|---|---|
| 7.0 TO 9.0 | 42 | 0 | 42 |
| > 9 | 8 | 0 | 8 |
| TOTAL | 100 | | |

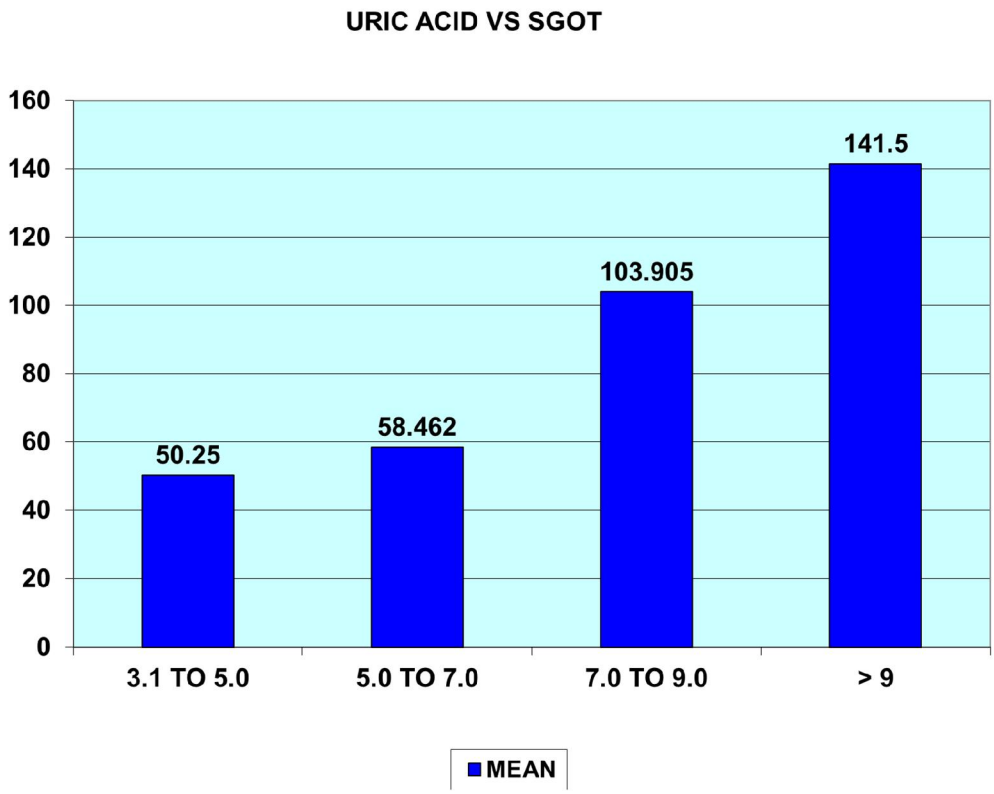



In this studied population hyper bilirubinemia associated with hyperuricemia which is significant. P value is <0.001

| | | BILIRUBIN | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 2.492 | 0.836 |
| 5.0 TO 7.0 | 26 | 2.788 | 1.493 |
| 7.0 TO 9.0 | 42 | 5.11 | 1.859 |

| | | | |
|---|---|---|---|
| > 9 | 8 | 4.425 | 2.241 |
| TOTAL | 100 | | |

< 0.001 Significant

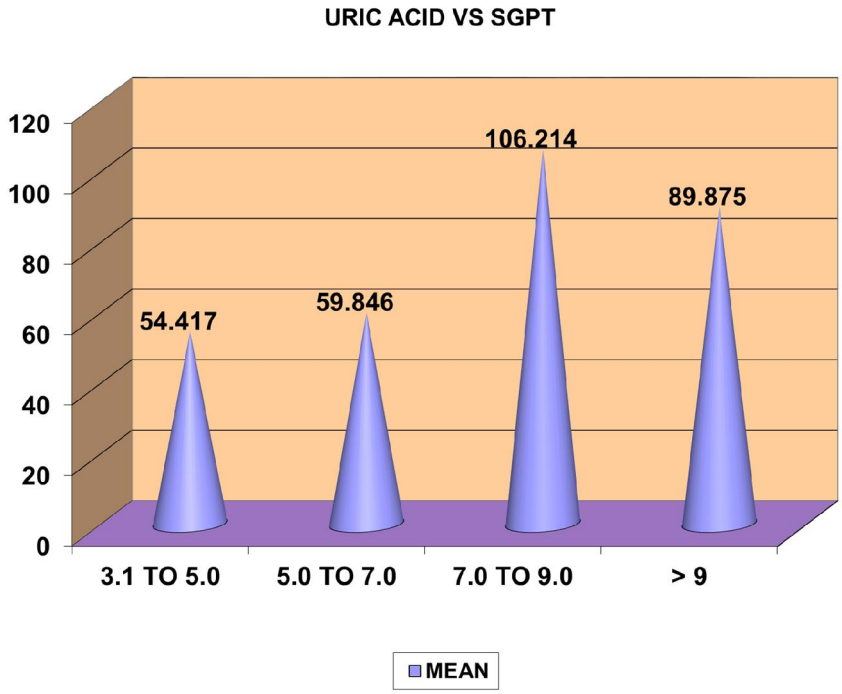



In this studied population increased SGOT levels associated with hyperuricemia which is significant. P value is <0.001

| | | SGOT | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 50.25 | 46.832 |
| 5.0 TO 7.0 | 26 | 58.462 | 23.261 |

| | | | |
|---|---|---|---|
| 7.0 TO 9.0 | 42 | 103.905 | 70.162 |
| > 9 | 8 | 141.5 | 158.98 |
| TOTAL | 100 | | |

< 0.001 Significant

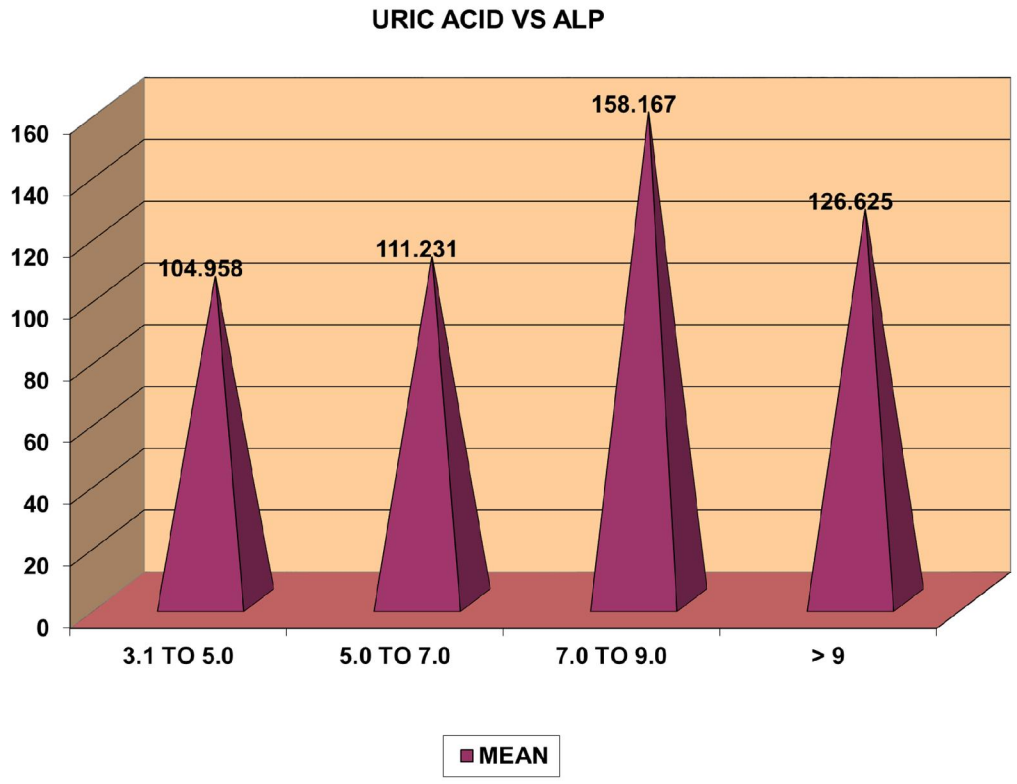



In this studied population increased SGPT levels associated with hyperuricemia which is significant. P value is <0.001

| | | | |
|---|---|---|---|
| | | SGPT | |

| URIC ACID | No of Cases | MEAN | Std Dev |
|---|---|---|---|
| 3.1 TO 5.0 | 24 | 54.417 | 19.662 |
| 5.0 TO 7.0 | 26 | 59.846 | 21.581 |
| 7.0 TO 9.0 | 42 | 106.214 | 51.984 |
| > 9 | 8 | 89.875 | 60.829 |
| TOTAL | 100 | | |

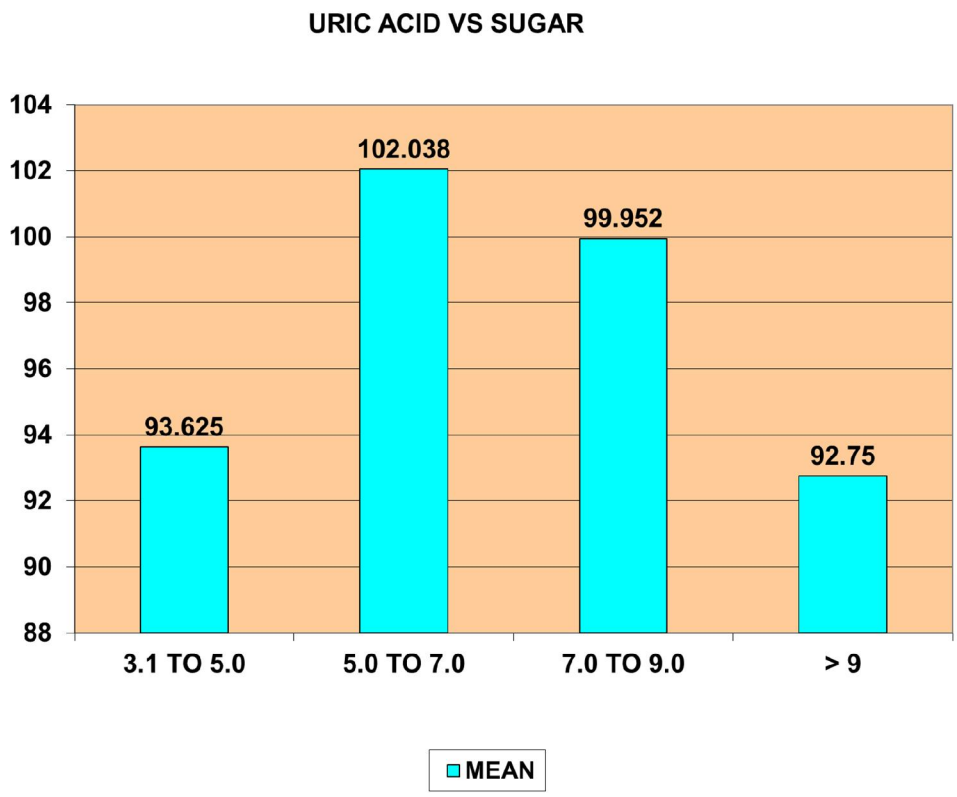
< 0.001 Significant



In this studied population increased alkaline phosphatase levels associated with hyperuricemia which is significant. P value is <0.001

| | | ALP | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 104.958 | 36.281 |
| 5.0 TO 7.0 | 26 | 111.231 | 40.522 |
| 7.0 TO 9.0 | 42 | 158.167 | 42.038 |
| > 9 | 8 | 126.625 | 84.356 |
| TOTAL | 100 | | |

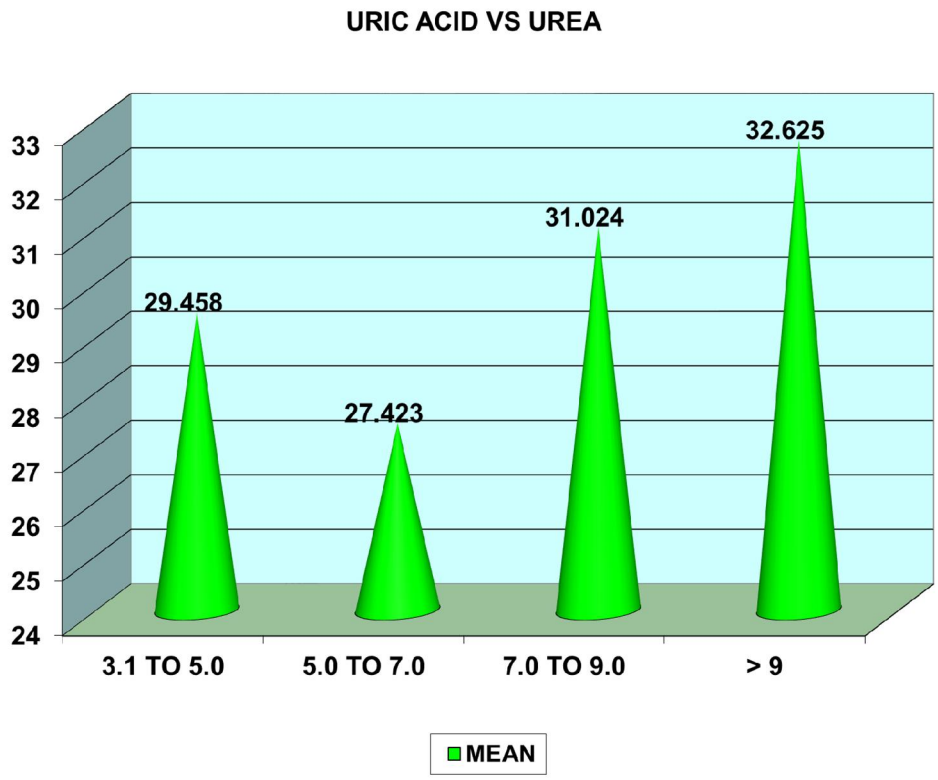
< 0.001 Significant




In this studied group blood sugar values not correlated with uric acid levels. P value not significant. P value is 0.148

| | | Sugar | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 93.625 | 11.776 |
| 5.0 TO 7.0 | 26 | 102.038 | 22.49 |
| 7.0 TO 9.0 | 42 | 99.952 | 8.859 |
| > 9 | 8 | 92.75 | 20.041 |
| TOTAL | 100 | | |

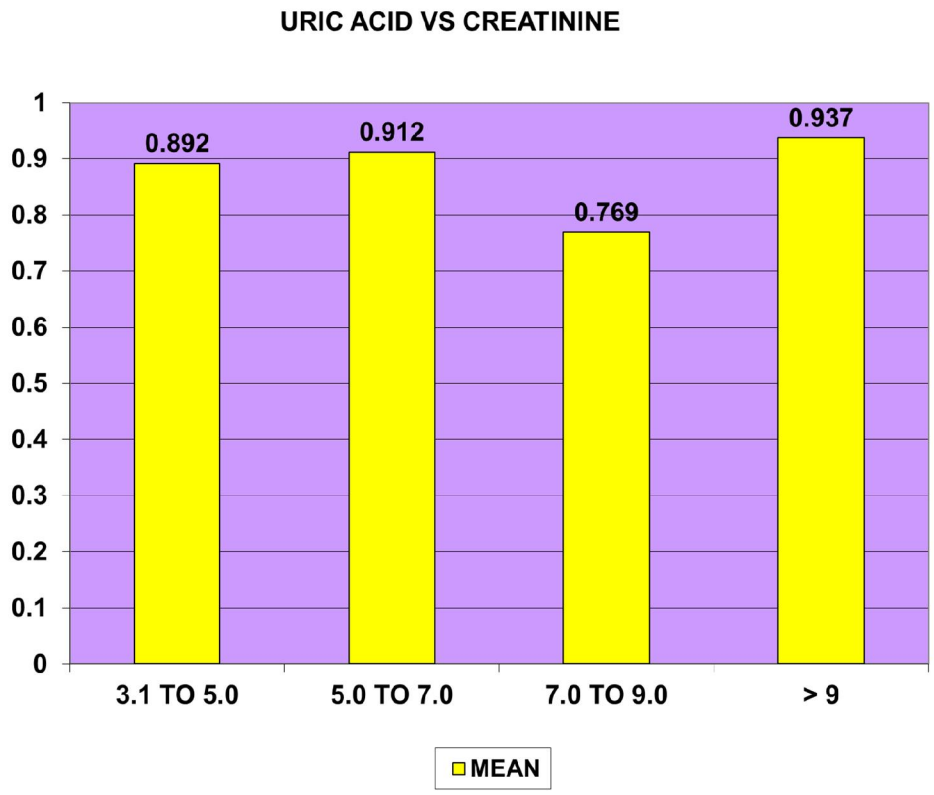
0.148 Not significant




In this studied population blood urea levels not correlated well with the uric acid levels. P value not significant (P value 0.094)

| | | Urea | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 29.458 | 7.095 |
| 5.0 TO 7.0 | 26 | 27.423 | 7.829 |
| 7.0 TO 9.0 | 42 | 31.024 | 5.493 |
| > 9 | 8 | 32.625 | 3.926 |
| TOTAL | 100 | | |

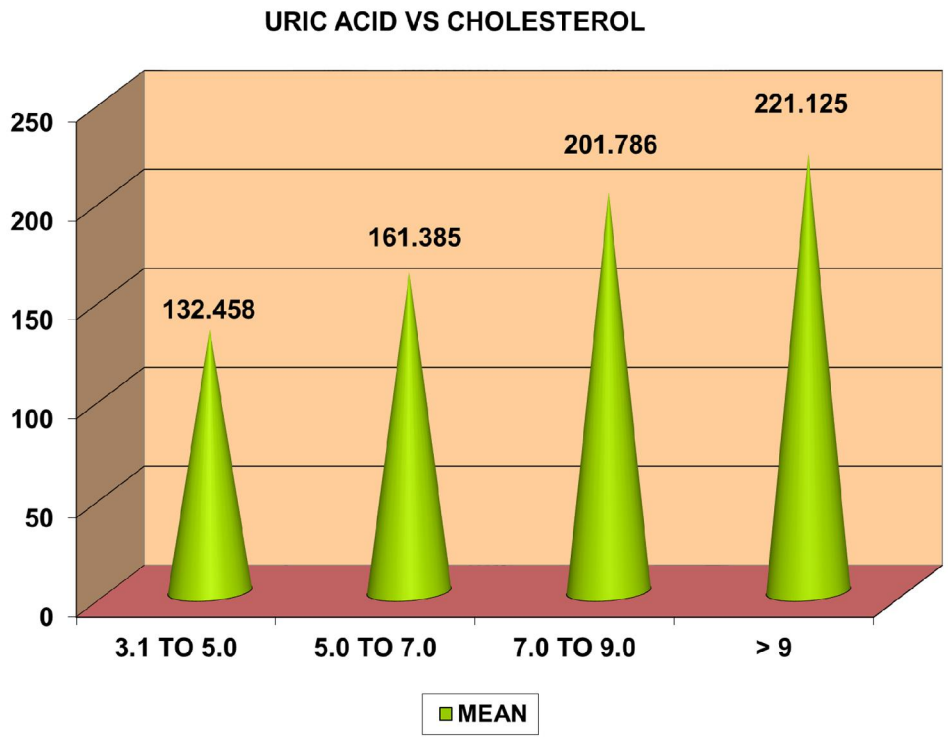
0.094 Not significant




In this studied group serum creatinine level not correlated with serum uric acid levels. P value 0.093 not significant

| | | Creatinine | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 0.892 | 0.301 |
| 5.0 TO 7.0 | 26 | 0.912 | 0.297 |
| 7.0 TO 9.0 | 42 | 0.769 | 0.199 |
| > 9 | 8 | 0.937 | 0.385 |
| TOTAL | 100 | | |

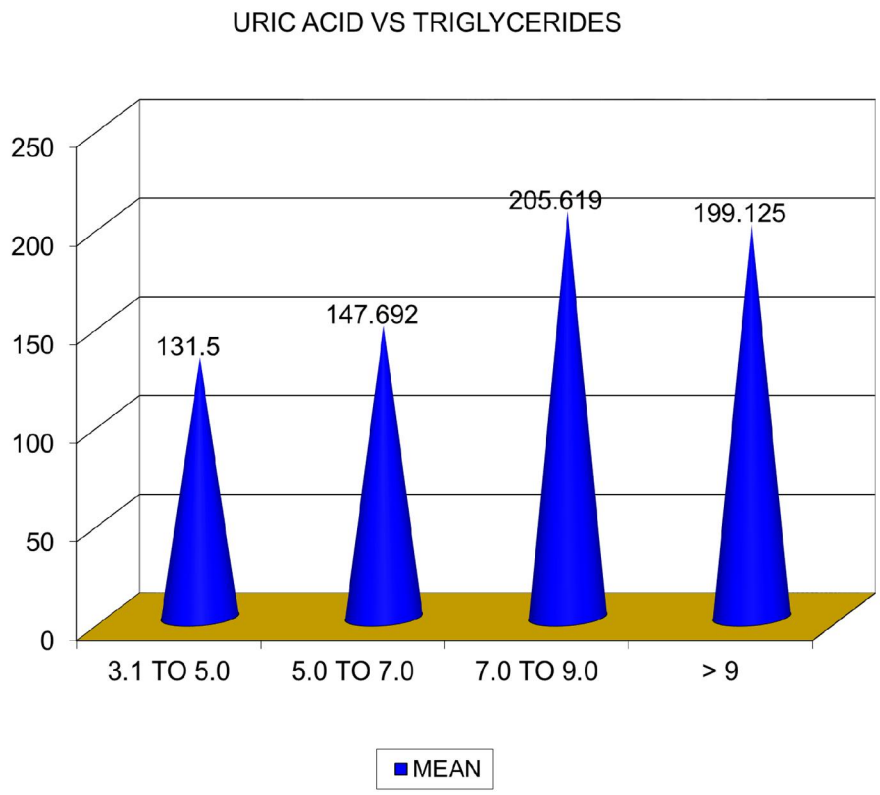
0.093 Not significant




In this study group hypercholesterolemia associated well with the increased uric acid levels. P value is significant. P value is <0.001

| | | Cholesterol | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 132.458 | 35.545 |
| 5.0 TO 7.0 | 26 | 161.385 | 37.709 |
| 7.0 TO 9.0 | 42 | 201.786 | 22.118 |
| > 9 | 8 | 221.125 | 39.226 |
| TOTAL | 100 | | |

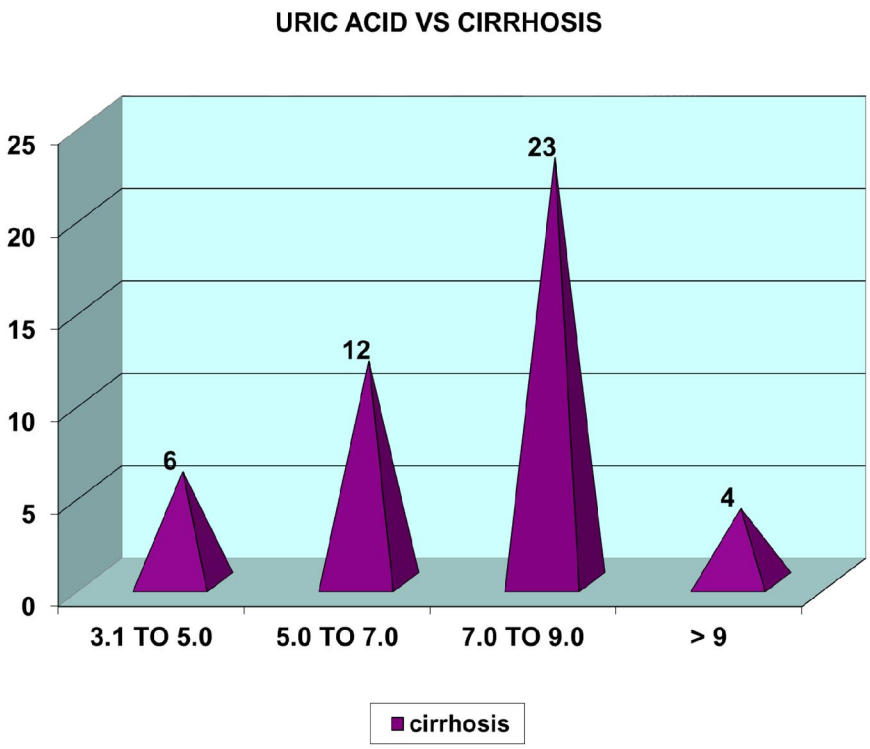
< 0.001 Significant




In this study increased levels of triglycerides associated with increased serum levels of uric acid. P value is significant (P <0.001)

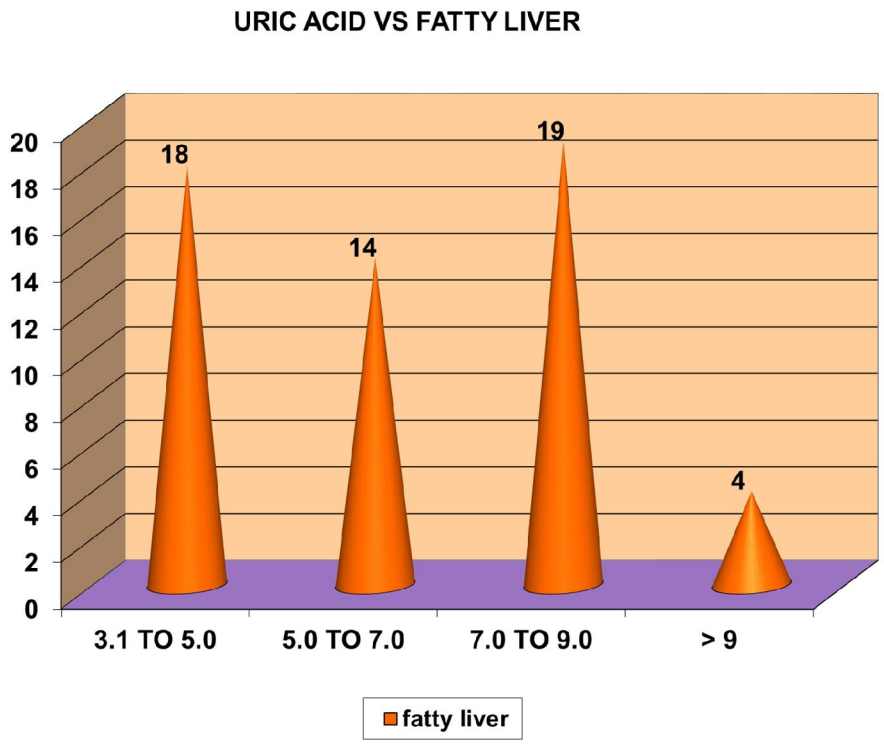
| | | Triglycerides | |
|---|---|---|---|
| URIC ACID | No of Cases | MEAN | Std Dev |
| 3.1 TO 5.0 | 24 | 131.5 | 27.707 |
| 5.0 TO 7.0 | 26 | 147.692 | 31.347 |
| 7.0 TO 9.0 | 42 | 205.619 | 46.098 |
| > 9 | 8 | 199.125 | 59.686 |
| TOTAL | 100 | | |

< 0.001 Significant




In this study population hyperuricemia associated with increased number of cases of cirrhosis. But the p value is 0.696 which is not significant

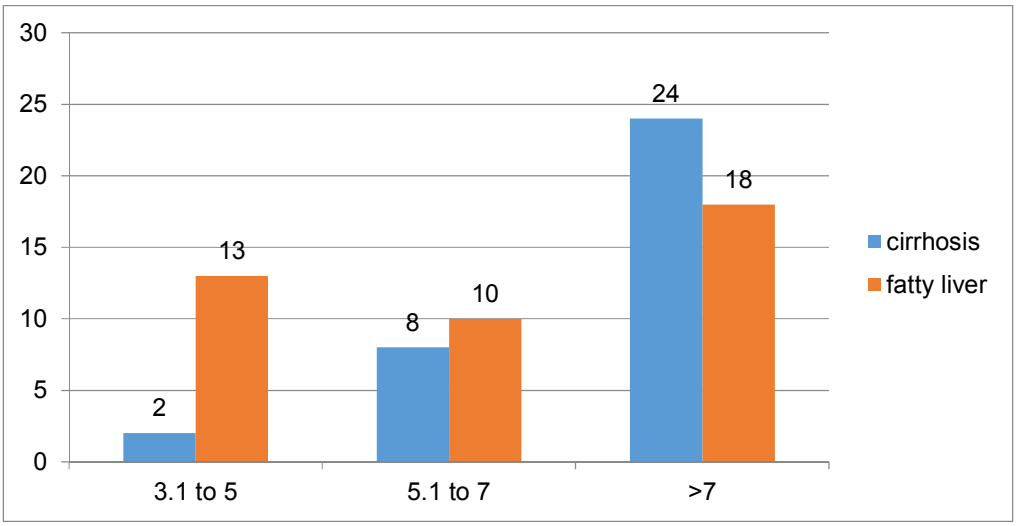
| URIC ACID | cirrhosis |
|---|---|
| 3.1 TO 5.0 | 6 |
| 5.0 TO 7.0 | 12 |
| 7.0 TO 9.0 | 23 |
| > 9 | 4 |




In this study increased number of patients seen both in lower and higher levels of uric acid. This has no clinical significance.

| URIC ACID | fatty liver |
|---|---|
| | |
| 3.1 TO 5.0 | 18 |
| 5.0 TO 7.0 | 14 |
| 7.0 TO 9.0 | 19 |
| > 9 | 4 |

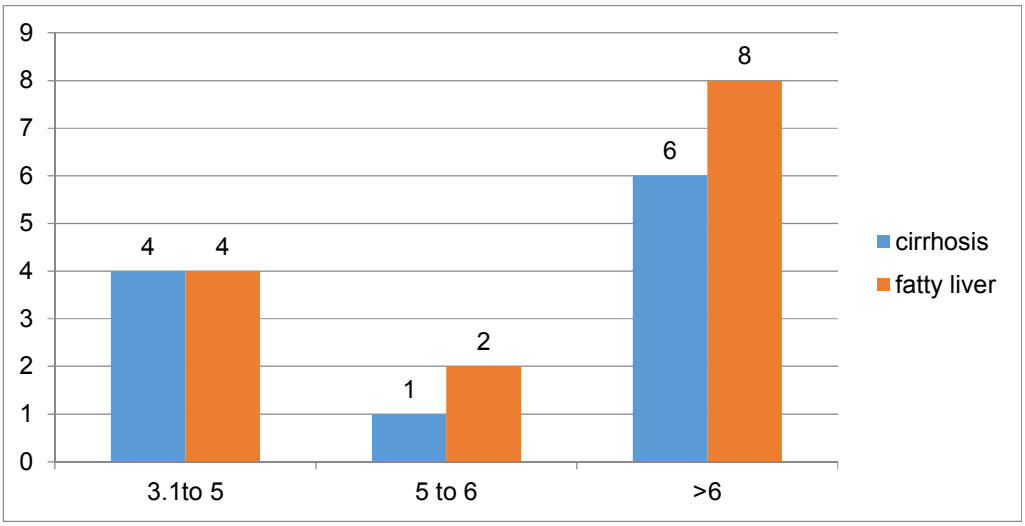
## ASSOCIATION OF CIRRHOSIS AND FATTY LIVER WITH URIC ACID IN MEN




In this study group male patients with increased levels of uric acid associated well with cirrhosis and fatty liver. This is significant

| Male | cirrhosis | fatty liver |
|---|---|---|
| uric acid | | |
| 3.1 to 5 | 2 | 13 |
| 5.1 to 7 | 8 | 10 |
| >7 | 24 | 18 |
| total | 34 | 41 |

## ASSOCIATION OF CIRRHOSIS AND FATTY LIVER WITH URIC ACID IN WOMEN




This study in female population had strong association with increased uric acid levels and cirrhosis and fatty liver. This is significant value

| female | cirrhosis | fatty liver |
|---|---|---|
| uric acid | | |
| 3.1to 5 | 4 | 4 |
| 5 to 6 | 1 | 2 |
| >6 | 6 | 8 |
| total | 11 | 14 |
| | | |

# DISCUSSION

## URIC ACID AND GENDER

Out of the 100 patients studied, the mean uric acid in the total population is 6.73, of which men had higher mean uric acid level when compared to female. But there was no statistical significance between these two groups.

## URIC ACID AND AGE

The mean age in the study group was 46.81years. The mean age for male are 47.52 years and the mean age for the female are 44.68 years. Men had higher mean age compared to women.

The mean age of onset of liver disease is higher in male compared to female. In our study it was observed that uric acid levels increase with age in male. But exact age group could not be identified.

## RISK FACTORS AND URIC ACID

In this study hyperbilirubinemia, hypercholesterolemia, BMI, waist circumference significantly associated with hyperuricemia.

Our study did not showed any positive correlation of smoking with hyperuricemia. Dharma et al has showed similar results.

Body mass index showed statistically significant association with uric acid levels. It was observed that subjects with BMI of 25 associated will with hyperuricemia.

South Asian people are more prone for development of cardiovascular disease even in the presence of lower BMI. This indicates that people with higher BMI have still more increase in the cardiovascular risk. Many studies done in this association of BMI with uric acid showed proven results.

According to our observation uric acid is useful in identifying cardiovascular risk in people with high BMI. In our study we have not included any risk factors. So hyperuricemia in high BMI is one the risk factors for the development of metabolic syndrome in future.

In our study we observed that nonalcoholic patients with ultrasonagram findings of cirrhosis had increased uric acid levels in both the sex. This clearly shows the association of hyperuricemia in cirrhosis. It indicates that in advanced liver diseases due to the oxidative stress and endothelial dysfunction serum uric acid level also increases.

In our study we also observed that people with fatty liver also had associated high uric acid levels. This shows that people with fatty liver and hyperuricemia in future may progress to the advanced liver disease, cirrhosis which is correlated well with the laboratory values of liver function tests.

# CONCLUSION

Uric acid is an old molecule with many new applications and it has also been studied in various metabolic diseases, cardiovascular diseases and chronic kidney disease. In this study it has been found that uric acid has a significant correlation with BMI, waist circumference and hypercholesterolemia.

Hyperuricemia is also associated with both alcoholic and nonalcoholic liver diseases due to increased oxidative stress and inflammatory actions. This study also concluded that hyperuricemia is associated with increased number of cases both with cirrhosis and fatty liver. This clearly indicates that hyperuricemia in fatty liver patients, who are nonalcoholic have considerable risk for future progression to cirrhosis of liver.

Because of its association with BMI, waist circumference and hypercholesterolemia, hyperuricemia may be considered as one the risk factor for metabolic syndrome.

## LIMITATIONS OF THE STUDY

In this study progression of the disease in both male and female age group could not be identified properly. We are also not able to correlate the association of other investigations like renal function tests. Ultrasonagram findings not well correlated with age and sex group. Further confirmation of the study needs liver biopsy.

## REFERENCES

1. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N England Journal Med 2008; 359:1811-1821.

2. Edwards NL. The role of hyperuricemia in vascular disorders. Current Rheumatology 2009; 21:132-137.

3. Sanyal AJ. The pathogenesis of NASH: human studies. In: Farrell FJ, George J, de la M, Hall P, McCulloch CE, eds. Fatty Liver Disease: NASH and Related Disorders. Malden, MA: Blackwell; 2005:76-90.

4. Moucari R, Asselah T, Cazals-Hatem D, Voitot H, Boyer N, Ripault MP, et al. Insulin resistance in chronic hepatitis C: association with genotypes

1 and 4, serum HCV RNA level, and liver fibrosis. Gastroenterology 2008; 134:416-423.

5. Centers for Disease Control and Prevention. The Third National Health and Nutrition Examination Survey (NHANES III 1988-1994) Reference Manuals and Reports [CD-ROM]. Bethesda, MD: National Center for Health Statistics; 1996.

6. Choi HK, Ford ES. Prevalence of the metabolic syndrome in individuals With hyperuricemia. Am J Med 2007; 120:442-447?

7. Nguyen S, Choi HK, Lusting RH, Hsu CY. Sugar-sweetened beverages,

Serum uric acid, and blood pressure in adolescents. J Pediatr 2009;154: 807-813.

8. NHANES 1999-2000 lab file. http://www.cdc.gov/nchs/nhanes/ lab99_00.htm. Accessed April 2010.

9. NHANES 2001-2002 lab file. http://www.cdc.gov/nchs/nhanes/2001-2002/lab01_02.htm. Accessed April 2010.

10. Boyko EJ, Lee SP. The prevalence and predictors of elevated Serum aminotransferase activity in the United States in 1999-2002. Am J Gastroenterology 2006; 101:76-82.

11. Ioannou GN, Weiss NS, Boyko EJ, Kahn SE, Lee SP. Contribution of Metabolic factors to alanine aminotransferase activity in persons with Other causes of liver disease. Gastroenterology 2005; 128:627-635.

12. Ioannou GN, Weiss NS, Boyko EJ, Mozaffarian D, Lee SP. Elevated Serum alanine aminotransferase activity and calculated risk of coronary Heart disease in the United States. HEPATOLOGY 2006; 43:1145-1151.

13. Ruhl CE, Everhart JE. Coffee and caffeine consumption reduce the Risk of elevated serum alanine aminotransferase activity in the United States. Gastroenterology 2005; 128:24-32.

14. Ruhl CE, Everhart JE. Elevated serum alanine aminotransferase and Gamma-glutamyltransferase and mortality in the United States population. Gastroenterology 2009; 136:477-485.

15. Ioannou GN, Weiss NS, Kowdley KV, Dominitz JA. Is obesity a risk Factor for cirrhosis-related death or hospitalization? A population-based Cohort study. Gastroenterology 2003; 125:1053-1059.

## ANNEXURES

## PROFORMA

## ABBREVATIONS

## MASTER CHART

## ASSOCIATION OF HIGH URIC ACID LEVELS IN CHRONIC LIVER DISEASE

# PROFORMA

## Medical unit

**Case No:**

**Name of the patient:**

**Sex: Age Ht Wt BMI Waist**

**History of present illness:**

**Past History:**

Diabetes mellitus

Hypertension

Ischemic Heart disease

Lung disease

Thyroid disease

Renal disease

Liver disease

**Drug History:**

Beta-blockers

Diuretics

Lipid lowering agents:

Steroids

**Personal History:**

Diet

Smoking

Alcohol

**Family History:**

CVD

HTN

Dyslipidemia

Diabetes

**GENERAL PHYSICAL EXAMINATION:**

Built

Pallor

Icterus

Clubbing

Oedema

Cyanosis

**VITALS:**

BP PR RR

**SYSTEMIC EXAMINATION:**

1. Respiratory System

2. Cardiovascular System

3. Abdominal System

4. Nervous System

**INVESTIGATION:**

**1.** LFT

2. RFT

3. Lipid profile

4 Serum Uric acid

5. Blood sugar

6. USG Abdomen

## ABBREVATIONS

NAFLD – Nonalcoholic liver disease

NASH – Nonalcoholic steato hepatitis

BMI – Body mass index

CLD – Chronic liver disease

UA – Uric acid

HCC – Hepato cellular carcinoma

ALD – Alcoholic liver disease

CHREBP – Carbohydrate, responsive element binding protein

VLDL – Very low density lipoproteins

MTP – Microsomal triglyceride transfer protein

NEFA – Non essential fatty acid

TGL – Triglycerides

HDL – High density lipoproteins

LDL – Low density lipoproteins

GGT- Gama glutamyl transferase

ALT – Alanine transaminase

AST – Aspartate transaminase

**MASTER CHART:**

| | Name | Age | Sex | BMI | WAIST | DM | HT | IHD | HYPOTHYROID | CKD | DRUGS | SMOKER | ALCOHOLIC | BILIRUBIN | DIRECT | INDIRECT | SGOT | SGPT | ALP | Sugar | Urea | Creatinine | Cholesterol | Triglycerides | USG | Uric acid |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | doivanai | 55 | female | 26.2 | 90 | na | na | na | na | na | na | na | na | 3 | 1 | 2 | 40 | 50 | 103 | 90 | 24 | 0.8 | 189 | 150 | cirrharir | 6.2 |
| 3 | mariammal | 60 | female | 25.1 | 88 | na | na | na | na | na | na | na | na | 1.7 | 0.7 | 1 | 62 | 80 | 66 | 64 | 36 | 1.6 | 194 | 169 | Fatty liver | 6.9 |
| 4 | marithai | 35 | female | 28 | 92 | na | na | na | na | na | na | na | na | 0.5 | 0.3 | 0.2 | 34 | 34 | 113 | 87 | 18 | 0.9 | 175 | 134 | cirrharir | 8.8 |
| 5 | jeyalakshmi | 40 | female | 27 | 88 | na | na | na | na | na | na | na | na | 2.5 | 1 | 1.5 | 20 | 17 | 41 | 111 | 19 | 0.8 | 148 | 98 | Fatty liver | 8.5 |
| 6 | indra | 49 | female | 25.4 | 90 | na | na | na | na | na | na | na | na | 3.8 | 1.3 | 2.5 | 445 | 85 | 55 | 88 | 28 | 0.8 | 189 | 169 | cirrharir | 7.2 |
| 7 | mariammal | 60 | female | 24.5 | 92 | na | na | na | na | na | na | na | na | 0.5 | 0.3 | 0.2 | 54 | 50 | 61 | 105 | 17 | 1.1 | 192 | 134 | Fatty liver | 6.3 |
| 8 | chandralekha | 35 | female | 23 | 82 | na | na | na | na | na | na | na | na | 0.7 | 0.3 | 0.4 | 132 | 28 | 39 | 103 | 18 | 0.9 | 165 | 110 | cirrharir | 5.1 |
| 9 | mariammal | 60 | female | 25.9 | 89 | na | na | na | na | na | na | na | na | 2.2 | 1 | 1.2 | 341 | 127 | 91 | 79 | 31 | 1.2 | 210 | 168 | Fatty liver | 7.6 |
| 10 | jathiraman | 40 | male | 26.8 | 87 | na | na | na | na | na | na | na | na | 5.2 | 2.3 | 2.9 | 106 | 47 | 26 | 113 | 38 | 1.7 | 184 | 169 | cirrharir | 9.2 |
| 11 | marahman | 56 | male | 27 | 94 | na | na | na | na | na | na | yes | na | 4.4 | 2.1 | 2.3 | 107 | 47 | 26 | 107 | 33 | 0.6 | 194 | 169 | Fatty liver | 9.9 |
| 12 | muruqalakshmi | 42 | female | 24.9 | 88 | na | na | na | na | na | na | na | na | 1.2 | 0.6 | 0.6 | 21 | 39 | 148 | 96 | 15 | 0.7 | 168 | 113 | cirrharir | 6.3 |
| 13 | guruchandran | 32 | male | 23.7 | 80 | na | na | na | na | na | na | na | na | 1.3 | 0.4 | 0.9 | 63 | 70 | 59 | 104 | 33 | 1 | 172 | 140 | cirrharir | 5.1 |
| 14 | arunachalam | 45 | male | 24.1 | 78 | na | na | na | na | na | na | yes | na | 1.8 | 0.9 | 0.9 | 264 | 113 | 175 | 103 | 19 | 0.8 | 168 | 138 | Fatty liver | 4.2 |
| 15 | pichaiah | 55 | male | 24.2 | 81 | na | na | na | na | na | na | na | na | 0.5 | 0.3 | 0.2 | 92 | 65 | 172 | 190 | 39 | 0.9 | 194 | 158 | cirrharir | 5.7 |
| 16 | valliammal | 56 | female | 23.9 | 79 | na | na | na | na | na | na | na | na | 0.9 | 0.4 | 0.5 | 40 | 30 | 70 | 90 | 17 | 1 | 110 | 105 | Fatty liver | 5.2 |
| 17 | balarubramanian | 45 | male | 28 | 94 | na | na | na | na | na | na | na | na | 1.6 | 0.7 | 0.9 | 19 | 58 | 78 | 105 | 23 | 1.3 | 182 | 188 | cirrharir | 8.3 |
| 18 | subramanian | 57 | male | 25.3 | 88 | na | na | na | na | na | na | na | na | 1.3 | 0.6 | 0.7 | 15 | 20 | 87 | 115 | 23 | 1.4 | 168 | 110 | Fatty liver | 6.3 |
| 19 | thirumalairamy | 54 | male | 27.5 | 93 | na | na | na | na | na | na | na | na | 27.6 | 11.7 | 16.1 | 528 | 190 | 216 | 65 | 37 | 1.2 | 228 | 198 | cirrharir | 9.9 |
| 20 | arumugam | 38 | male | 23 | 82 | na | na | na | na | na | na | na | na | 36.9 | 15 | 21.9 | 49 | 19 | 32 | 81 | 32 | 0.5 | 193 | 154 | cirrharir | 5.3 |
| 21 | thilagar | 50 | male | 25.6 | 87 | na | na | na | na | na | na | yes | na | 0.6 | 0.3 | 0.3 | 32 | 32 | 149 | 100 | 35 | 1.2 | 173 | 60 | cirrharir | 7.6 |
| 22 | chellaiah | 60 | male | 27.8 | 96 | na | na | na | na | na | na | yes | na | 0.5 | 0.3 | 0.2 | 27 | 16 | 67 | 100 | 32 | 1.1 | 168 | 98 | Fatty liver | 10.3 |
| 23 | paamiraj | 32 | male | 22 | 75 | na | na | na | na | na | na | na | na | 25.6 | 10.4 | 15.2 | 60 | 75 | 51 | 86 | 37 | 1 | 210 | 196 | Fatty liver | 3.3 |
| 24 | albertraj | 35 | male | 23.1 | 78 | na | na | na | na | na | na | na | na | 3.2 | 0.6 | 2.6 | 16 | 19 | 46 | 76 | 30 | 0.6 | 198 | 164 | cirrharir | 4.3 |
| 25 | paramasivan | 43 | male | 23.6 | 80 | na | na | na | na | na | na | na | na | 9.5 | 4.2 | 5.3 | 108 | 392 | 57 | 110 | 30 | 0.8 | 190 | 210 | cirrharir | 7.1 |
| 26 | muppidathi | 60 | male | 28 | 94 | na | na | na | na | na | na | na | na | 3.4 | 1.4 | 2 | 55 | 44 | 81 | 60 | 32 | 0.6 | 210 | 188 | Fatty liver | 10.3 |
| 27 | arakki | 37 | male | 23.7 | 81 | na | na | na | na | na | na | na | na | 2.3 | 0.8 | 1.5 | 30 | 47 | 143 | 73 | 20 | 1.4 | 160 | 110 | cirrharir | 4.8 |
| 28 | mala | 22 | female | 25.2 | 83 | na | na | na | na | na | na | na | na | 1.4 | 0.4 | 1 | 26 | 68 | 44 | 93 | 18 | 1.7 | 168 | 98 | Fatty liver | 4.6 |
| 29 | parunkili | 35 | female | 26 | 92 | na | na | na | na | na | na | na | na | 0.9 | 0.4 | 0.5 | 0.5 | 57 | 119 | 99 | 16 | 0.8 | 178 | 154 | cirrharir | 6.7 |
| 30 | thambidurai | 56 | male | 23.7 | 82 | na | na | na | na | na | na | na | na | 2.8 | 1.2 | 1.6 | 40 | 35 | 167 | 110 | 15 | 1.1 | 210 | 189 | Fatty liver | 5.4 |
| 31 | dhoonathayalan | 50 | male | 25.2 | 86 | na | na | na | na | na | na | yes | na | 9.5 | 4.4 | 5.1 | 168 | 57 | 155 | 109 | 20 | 1 | 164 | 138 | Fatty liver | 6.8 |
| 32 | arakkimuthu | 40 | male | 24.9 | 81 | na | na | na | na | na | na | yes | na | 4 | 1.3 | 2.7 | 95 | 53 | 96 | 103 | 37 | 1.6 | 194 | 188 | Fatty liver | 5.8 |
| 33 | abraham | 60 | male | 24 | 78 | na | na | na | na | na | na | yes | na | 0.9 | 0.6 | 0.3 | 29 | 48 | 134 | 75 | 27 | 1.7 | 168 | 110 | Fatty liver | 4.7 |
| 34 | ramammal | 47 | female | 23.2 | 76 | na | na | na | na | na | na | na | na | 2 | 0.6 | 1.4 | 29 | 39 | 107 | 75 | 25 | 0.7 | 168 | 176 | Fatty liver | 4.8 |
| 35 | muruqalakshmi | 42 | female | 24.2 | 77 | na | na | na | na | na | na | na | na | 1.2 | 0.6 | 0.6 | 21 | 39 | 148 | 116 | 15 | 0.7 | 168 | 131 | cirrharir | 4.8 |
| 36 | muruqaran | 45 | male | 23 | 79 | na | na | na | na | na | na | na | na | 1.2 | 0.6 | 0.6 | 42 | 36 | 68 | 110 | 26 | 0.6 | 168 | 189 | Fatty liver | 4.9 |
| 37 | vembu | 38 | male | 25 | 84 | na | na | na | na | na | na | yes | na | 2.8 | 1.6 | 1.2 | 48 | 40 | 88 | 100 | 32 | 0.9 | 198 | 175 | Fatty liver | 5.2 |
| 38 | karuppuramy | 60 | male | 23.9 | 82 | na | na | na | na | na | na | yes | na | 3.8 | 2.4 | 1.4 | 54 | 62 | 92 | 100 | 34 | 1.2 | 210 | 180 | cirrharir | 6.8 |
| 39 | elanqa | 60 | male | 26.5 | 87 | na | na | na | na | na | na | yes | na | 6.2 | 4.6 | 1.6 | 88 | 82 | 110 | 111 | 36 | 1.2 | 184 | 170 | cirrharir | 7.4 |
| 40 | ravoondran | 43 | male | 25.1 | 90 | na | na | na | na | na | na | yes | na | 3.1 | 1.9 | 1.2 | 84 | 88 | 103 | 88 | 31 | 0.9 | 96 | 116 | cirrharir | 5.5 |
| 41 | thiraviyam | 42 | male | 23.7 | 79 | na | na | na | na | na | na | na | na | 2.1 | 1.1 | 1 | 42 | 40 | 56 | 94 | 33 | 0.8 | 110 | 123 | Fatty liver | 4.9 |
| 42 | pitchiah | 58 | male | 25.8 | 104 | na | na | na | na | na | na | na | na | 5.9 | 3.8 | 2.1 | 98 | 100 | 128 | 98 | 28 | 0.7 | 198 | 167 | cirrharir | 7.7 |
| 43 | harisankar | 38 | male | 24.8 | 98 | na | na | na | na | na | na | na | na | 4.1 | 2.1 | 2 | 68 | 78 | 145 | 104 | 29 | 0.6 | 154 | 168 | cirrharir | 6.2 |
| 44 | donnirh | 46 | male | 25.4 | 100 | na | na | na | na | na | na | yes | na | 3.8 | 2.2 | 1.6 | 88 | 86 | 152 | 110 | 32 | 0.7 | 190 | 179 | Fatty liver | 7.2 |
| 45 | kumar | 36 | male | 24 | 90 | na | na | na | na | na | na | na | na | 2.2 | 1.1 | 1.1 | 54 | 56 | 130 | 103 | 37 | 0.9 | 109 | 154 | Fatty liver | 5 |
| 46 | oliva | 49 | male | 26 | 104 | na | na | na | na | na | na | na | na | 3.4 | 2.4 | 1 | 95 | 98 | 158 | 87 | 28 | 0.6 | 202 | 198 | Fatty liver | 7.6 |
| 47 | arumugam | 40 | male | 27 | 101 | na | na | na | na | na | na | yes | na | 3.8 | 2.6 | 1.2 | 86 | 94 | 160 | 104 | 26 | 0.7 | 200 | 185 | Fatty liver | 7.3 |
| 47 | arumugam | 40 | male | 27 | 101 | na | na | na | na | na | yes | na | 3.8 | 2.6 | 1.2 | 86 | 94 | 160 | 104 | 26 | 0.7 | 200 | 185 | Fatty liver | 7.3 |
| 48 | annaraimuthu | 32 | male | 26.1 | 103 | na | na | na | na | na | yes | na | 4.4 | 2.2 | 2.2 | 90 | 96 | 164 | 96 | 27 | 0.7 | 238 | 203 | Fatty liver | 8.1 |
| 49 | nithiyananthan | 50 | male | 23 | 89 | na | na | na | na | na | na | na | na | 3.2 | 2.2 | 1 | 57 | 58 | 121 | 88 | 36 | 0.8 | 110 | 143 | cirrharir | 4.9 |
| 50 | pirati | 30 | female | 22.6 | 79 | na | na | na | na | na | na | na | na | 2.5 | 1.3 | 1.2 | 42 | 46 | 120 | 93 | 37 | 0.9 | 98 | 121 | Fatty liver | 3.7 |
| 51 | muthulakshmi | 55 | female | 25.6 | 94 | na | na | na | na | na | na | na | na | 4.8 | 2.8 | 2 | 99 | 96 | 148 | 103 | 39 | 0.7 | 187 | 165 | cirrharir | 7.3 |
| 52 | dovadar | 45 | male | 26 | 104 | na | na | na | na | na | na | yes | na | 4.9 | 3.2 | 5 | 78 | 89 | 160 | 109 | 36 | 0.8 | 208 | 219 | Fatty liver | 8.6 |
| 53 | dhayalan | 57 | male | 24.8 | 100 | na | na | na | na | na | na | yes | na | 3.6 | 1.8 | 1.8 | 46 | 66 | 147 | 89 | 36 | 0.5 | 169 | 188 | cirrharir | 6.2 |
| 54 | arumugam | 43 | male | 24 | 96 | na | na | na | na | na | na | na | na | 2.1 | 1.1 | 1 | 43 | 43 | 110 | 96 | 37 | 0.7 | 102 | 123 | Fatty liver | 4.5 |
| 55 | venkatachalam | 43 | male | 23.6 | 90 | na | na | na | na | na | na | yes | na | 4.2 | 2.2 | 2 | 52 | 68 | 140 | 106 | 28 | 0.5 | 156 | 176 | cirrharir | 6.5 |
| 56 | baamiraj | 32 | male | 25.1 | 105 | na | na | na | na | na | na | yes | na | 3.9 | 2.9 | 1 | 95 | 102 | 169 | 103 | 27 | 0.6 | 208 | 234 | Fatty liver | 8 |
| 57 | mydeenpitchai | 42 | male | 24.9 | 103 | na | na | na | na | na | na | yes | na | 5.5 | 3.5 | 2 | 78 | 98 | 140 | 96 | 39 | 1 | 199 | 203 | cirrharir | 7.7 |
| 58 | mahamedmydeen | 48 | male | 25.2 | 105 | na | na | na | na | na | na | yes | na | 4.9 | 3.6 | 1.3 | 99 | 104 | 178 | 89 | 31 | 0.8 | 229 | 234 | Fatty liver | 9 |
| 59 | muppidathi | 60 | male | 23.9 | 91 | na | na | na | na | na | na | na | na | 2.3 | 1.2 | 1.1 | 43 | 45 | 89 | 85 | 34 | 0.8 | 119 | 126 | Fatty liver | 3.9 |
| 60 | ramasamy | 59 | male | 24.8 | 101 | na | na | na | na | na | na | na | na | 4.7 | 3.2 | 1.5 | 96 | 98 | 156 | 94 | 26 | 0.7 | 216 | 267 | Fatty liver | 8.5 |
| 61 | subbulakshmi | 60 | female | 26 | 94 | na | na | na | na | na | na | na | na | 5.1 | 3.9 | 1.3 | 99 | 104 | 172 | 96 | 33 | 0.9 | 223 | 287 | Fatty liver | 8.3 |
| 62 | antonyraj | 45 | male | 25 | 106 | na | na | na | na | na | na | yes | na | 6.7 | 4.5 | 2.2 | 88 | 92 | 162 | 103 | 32 | 0.6 | 209 | 240 | cirrharir | 8.2 |
| 63 | zylappan | 49 | male | 24.9 | 101 | na | na | na | na | na | na | na | na | 6 | 4 | 2 | 102 | 105 | 189 | 107 | 30 | 1 | 199 | 213 | cirrharir | 7.5 |
| 64 | panchammal | 37 | male | 23.7 | 94 | na | na | na | na | na | na | na | na | 2.6 | 1.8 | 0.8 | 43 | 44 | 88 | 111 | 24 | 0.9 | 189 | 134 | Fatty liver | 4.2 |
| 65 | rajasingh | 45 | male | 25.5 | 104 | na | na | na | na | na | na | yes | na | 5.8 | 3.8 | 2 | 98 | 107 | 189 | 103 | 26 | 0.8 | 203 | 256 | cirrharir | 9.1 |
| 66 | palramy | 53 | male | 24.1 | 97 | na | na | na | na | na | na | na | na | 3.2 | 2.4 | 0.8 | 43 | 46 | 88 | 91 | 25 | 0.7 | 112 | 125 | Fatty liver | 3.8 |
| 67 | lila | 29 | female | 24 | 88 | na | na | na | na | na | na | na | na | 2.9 | 1.6 | 1.3 | 43 | 45 | 78 | 88 | 29 | 0.6 | 98 | 110 | Fatty liver | 3.1 |
| 68 | potchiammal | 37 | female | 25.6 | 96 | na | na | na | na | na | na | na | na | 5.4 | 3.7 | 1.7 | 87 | 99 | 168 | 83 | 33 | 0.6 | 203 | 199 | Fatty liver | 8.7 |
| 69 | ramasamy | 49 | male | 25.2 | 105 | na | na | na | na | na | na | yes | na | 5.3 | 3.6 | 1.7 | 98 | 106 | 190 | 93 | 35 | 0.5 | 267 | 250 | Fatty liver | 9 |
| 70 | chellammal | 55 | female | 23 | 82 | na | na | na | na | na | na | na | na | 3.4 | 2.4 | 1 | 44 | 49 | 89 | 107 | 33 | 0.8 | 102 | 130 | cirrharir | 3.8 |
| 71 | muruqan | 36 | male | 23.5 | 95 | na | na | na | na | na | na | na | na | 2.8 | 1.6 | 1.2 | 46 | 52 | 90 | 101 | 30 | 0.7 | 113 | 145 | Fatty liver | 3.9 |
| 72 | subramanian | 60 | male | 24 | 100 | na | na | na | na | na | na | yes | na | 6.4 | 4.8 | 1.6 | 90 | 103 | 196 | 104 | 27 | 0.6 | 199 | 242 | cirrharir | 8.1 |
| 73 | balamuruqan | 39 | male | 24.6 | 101 | na | na | na | na | na | na | na | na | 5.5 | 3.3 | 2.2 | 108 | 110 | 190 | 105 | 40 | 0.9 | 202 | 211 | Fatty liver | 8.8 |
| 74 | manivel | 58 | male | 24.9 | 102 | na | na | na | na | na | na | yes | na | 6.8 | 4.4 | 2.4 | 99 | 105 | 184 | 112 | 29 | 0.6 | 210 | 234 | cirrharir | 8.3 |
| 75 | arakkiammal | 57 | female | 23.7 | 84 | na | na | na | na | na | na | na | na | 3.6 | 2.6 | 1 | 45 | 67 | 132 | 97 | 35 | 0.9 | 112 | 101 | cirrharir | 4.9 |
| 76 | sivaperumal | 41 | male | 24.2 | 93 | na | na | na | na | na | na | na | na | 3.4 | 2.5 | 0.9 | 52 | 68 | 122 | 86 | 36 | 0.6 | 111 | 102 | Fatty liver | 5.1 |
| 77 | balarubramanian | 55 | male | 25.2 | 104 | na | na | na | na | na | na | yes | na | 7.9 | 4.8 | 3.1 | 100 | 119 | 190 | 106 | 29 | 0.9 | 246 | 234 | cirrharir | 9.7 |
| 78 | sankarapandiyan | 52 | male | 25.3 | 103 | na | na | na | na | na | na | na | na | 6.8 | 3.9 | 2.9 | 92 | 109 | 183 | 110 | 36 | 0.8 | 234 | 289 | cirrharir | 8.6 |
| 79 | selvan | 42 | male | 24.6 | 99 | na | na | na | na | na | na | yes | na | 4.5 | 2.9 | 1.6 | 106 | 118 | 190 | 101 | 29 | 0.6 | 212 | 267 | Fatty liver | 8.9 |
| 80 | syed alifathima | 28 | female | 26.7 | 92 | na | na | na | na | na | na | na | na | 3.9 | 2.7 | 1.2 | 99 | 106 | 167 | 90 | 33 | 0.8 | 199 | 210 | Fatty liver | 7.5 |
| 81 | selvakumar | 46 | male | 24.5 | 90 | na | na | na | na | na | na | yes | na | 6.7 | 4.5 | 2.2 | 79 | 95 | 156 | 86 | 39 | 1 | 178 | 203 | cirrharir | 7.5 |
| 82 | muthukumar | 43 | male | 24.1 | 94 | na | na | na | na | na | na | yes | na | 3.9 | 2.6 | 1.3 | 56 | 86 | 143 | 96 | 36 | 0.9 | 99 | 101 | Fatty liver | 4.8 |
| 83 | jathiraman | 40 | male | 25.2 | 100 | na | na | na | na | na | na | na | na | 4.9 | 3.1 | 1.8 | 107 | 134 | 206 | 102 | 27 | 0.7 | 202 | 256 | Fatty liver | 8.3 |
| 84 | ramasamy | 58 | male | 25.2 | 105 | na | na | na | na | na | na | yes | na | 6.7 | 4.3 | 2.4 | 87 | 97 | 167 | 105 | 33 | 0.6 | 198 | 210 | cirrharir | 7.8 |
| 85 | muthusamy | 42 | male | 24.4 | 98 | na | na | na | na | na | na | na | na | 4.5 | 2.8 | 1.7 | 90 | 102 | 189 | 92 | 30 | 0.6 | 201 | 189 | Fatty liver | 7.8 |
| 86 | samuval | 60 | male | 24.9 | 101 | na | na | na | na | na | na | yes | na | 7.9 | 5.2 | 3.7 | 110 | 156 | 200 | 106 | 37 | 0.7 | 256 | 298 | cirrharir | 8.2 |
| 87 | indira | 30 | female | 23 | 78 | na | na | na | na | na | na | na | na | 3.9 | 2.6 | 1.3 | 46 | 78 | 139 | 100 | 40 | 1 | 100 | 110 | Fatty liver | 4.2 |
| 88 | arakkiammal | 42 | female | 25.2 | 88 | na | na | na | na | na | na | na | na | 4.8 | 2.8 | 2 | 59 | 94 | 149 | 102 | 38 | 0.9 | 188 | 199 | Fatty liver | 6.9 |
| 89 | qanaran | 47 | male | 24.9 | 101 | na | na | na | na | na | na | na | na | 5.1 | 3.8 | 1.3 | 112 | 120 | 190 | 102 | 23 | 0.7 | 222 | 213 | Fatty liver | 8.9 |
| 90 | ravindran | 60 | male | 24.7 | 99 | na | na | na | na | na | na | yes | na | 6.2 | 4.2 | 2 | 97 | 113 | 176 | 98 | 28 | 0.5 | 188 | 199 | cirrharir | 7.4 |
| 91 | vembu | 51 | male | 24.8 | 100 | na | na | na | na | na | na | na | na | 6.4 | 4.2 | 2.2 | 95 | 110 | 171 | 110 | 25 | 0.9 | 180 | 192 | cirrharir | 7.5 |
| 92 | hariharan | 40 | male | 23.9 | 93 | na | na | na | na | na | na | yes | na | 4.3 | 2.3 | 2 | 65 | 86 | 151 | 102 | 27 | 0.8 | 98 | 100 | Fatty liver | 5.7 |
| 93 | nallathambi | 26 | male | 25.2 | 104 | na | na | na | na | na | na | na | na | 5.5 | 3.3 | 2.2 | 103 | 149 | 210 | 88 | 34 | 0.6 | 256 | 289 | Fatty liver | 9.2 |

| | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 91 | vembu | 51 | male | 24.8 | 100 | na | na | na | na | na | na | na | na | 6.4 | 4.2 | 2.2 | 95 | 110 | 171 | 110 | 25 | 0.9 | 100 | 192 | cirrhosis | 7.5 |
| 92 | hariharan | 40 | male | 23.9 | 93 | na | na | na | na | na | yes | na | na | 4.3 | 2.3 | 2 | 65 | 86 | 151 | 102 | 27 | 0.8 | 90 | 100 | fatty liver | 5.7 |
| 93 | nallathambi | 26 | male | 25.2 | 104 | na | na | na | na | na | na | na | na | 5.5 | 3.3 | 2.2 | 103 | 149 | 210 | 88 | 34 | 0.6 | 256 | 289 | fatty liver | 9.2 |
| 94 | paul durai | 57 | male | 24.9 | 100 | na | na | na | na | na | yes | na | na | 6.9 | 4.6 | 2.3 | 112 | 124 | 198 | 92 | 35 | 0.5 | 212 | 204 | cirrhosis | 8.4 |
| 95 | narayanan | 60 | male | 24.8 | 99 | na | na | na | na | na | na | na | na | 6.7 | 4.5 | 2.2 | 104 | 112 | 179 | 96 | 37 | 0.7 | 199 | 192 | cirrhosis | 8.1 |
| 96 | rajagopal | 55 | male | 25.2 | 105 | na | na | na | na | na | na | na | na | 7.5 | 4.9 | 2.6 | 107 | 135 | 197 | 108 | 38 | 0.6 | 170 | 189 | cirrhosis | 8 |
| 97 | veerapathiran | 60 | male | 24.9 | 96 | na | na | na | na | na | na | na | na | 5.8 | 3.3 | 2.5 | 99 | 110 | 176 | 109 | 27 | 0.7 | 170 | 198 | cirrhosis | 7.9 |
| 98 | kanthasamy | 49 | male | 23.9 | 92 | na | na | na | na | na | yes | na | na | 3.2 | 2 | 1.2 | 56 | 78 | 130 | 104 | 29 | 0.8 | 123 | 167 | fatty liver | 5.6 |
| 99 | amaran | 36 | male | 23.7 | 92 | na | na | na | na | na | na | na | na | 3.9 | 2.6 | 1.3 | 59 | 89 | 145 | 101 | 26 | 0.7 | 103 | 138 | fatty liver | 6 |
| 100 | muthiya | 54 | male | 24 | 90 | na | na | na | na | na | yes | na | na | 2.5 | 1.3 | 1.2 | 42 | 67 | 110 | 90 | 24 | 0.8 | 110 | 98 | fatty liver | 3.7 |
| 101 | muthulakshmi | 48 | female | 24.5 | 84 | na | na | na | na | na | na | na | na | 2.9 | 1.5 | 1.4 | 48 | 78 | 98 | 88 | 25 | 0.9 | 99 | 111 | fatty liver | 5.5 |