Lipid Associated Disorders

OR

Lipid Related Clinical Problems

- **Obesity- Metabolic Syndrome**
  - Dyslipoproteinemias/Dyslipidemias
  - Fatty Liver
  - Atherosclerosis
  - Coronary Heart Diseases
  - Myocardial Infarction
  - Stroke

Causes of Lipid Associated Disorders

- **Diseases associated with abnormal lipid concentrations may be due to:**
  - **Nutritional Imbalances**
  - **Lifestyle habits**
  - **Genetic abnormalities**
  - **Secondary causes as a consequence of other disease**

Disorders Of Lipoproteins

Dyslipoproteinemias/Dyslipidemias

Types Of Lipoprotein Disorders

Hyperlipoproteinemias
And
Hypolipoproteinemias

Dyslipoproteinemias/ Dyslipidemias

- **Dyslipoproteinemias** can be subdivided into two major categories

1. **Hyperlipoproteinemias**
   - Hypercholesterolemia
   - Hypertriglyceridemia
   - Combined Hyperlipoproteinemia
2. **Hypolipoproteinemias**

Hyperlipoproteinemia

- Hyperlipoproteinemia is an **abnormal condition**

- With an **increased abnormal levels of circulating Lipoproteins** in **blood**.

Dyslipidemias

- Dyslipidemias are due **to defect in Lipoprotein metabolism**

- May include **both excess and deficiency of Lipoproteins**.

- Associated mostly **in increase of one or more Lipid forms in blood circulation**.

Classification Of Dyslipidemias

Based On Number Of Gene Involvement

Primary Hyperlipoproteinemia

- Monogenic defect
- Polygenic Defect

Monogenic Disorders

- **Familial Hypercholesterolemia**
  - Homozygous or Heterozygous
  - Defect: inactive LDL receptor
- **Familial Lipoprotein Lipase deficiency**
  - Defect: inactive lipoprotein lipase
- **Familial combined Hyperlipidemia**
  - Defect: Unknown

Polygenic/Multifactorial

- These are commonly encountered
  - Hypercholesterolemia
  - Hypertriglyceridemia

Causes Of Dyslipoproteinemias/ Dyslipidemias

- Dyslipidemias are generally caused by **impaired Lipoprotein metabolism :**
  - **Biosynthesis (Increased)**
  - **Transformation and Transport (Improper)**
  - **Uptake and Utilization (Decreased)**

Causes of Hyperlipoproteinemia

- **Increased formation of Lipoprotein**
- **Reduced clearance of LP from circulation**
  - **Factors Causing These**
    - **Excessive dietary intake of Carbs and Lipids**
    - **Biochemical defects in LP metabolism**
    - **Deficient Protein to form Apoproteins**
    - **Defect in Enzymes and Proteins Associated to LP**
    - **Defect in Receptors for LP**
    - **Use of drugs that perturb LP formation or catabolism**

Hereditary Causes of Hyperlipidemia

- Familial Hypercholesterolemia
  - Codominant genetic disorder, coccurs in heterozygous form
  - Occurs in 1 in 500 individuals
  - Mutation in LDL receptor, resulting in elevated levels of LDL at birth and throughout life
  - High risk for atherosclerosis, tendon xanthomas (75% of patients), tuberous xanthomas and xanthelasmas of eyes.
- Familial Combined Hyperlipidemia
  - Autosomal dominant
  - Increased secretions of VLDLs
- Dysbetalipoproteinemia
  - Affects 1 in 10,000
  - Results in apo E2, a binding-defective form of apoE (which usually plays important role in catabolism of chylomicron and VLDL)
  - Increased risk for atherosclerosis, peripheral vascular disease
  - Tuberous xanthomas, striae palmaris

Genetic Causes of Dyslipidemia

Disease	Lipid Profile	Prevalence	Etiology
Primary Hypercholesterolemia			
Familial Hypercholesterolemia	↑↑ LDL	1:500 (+/-)	↓ LDL Receptor
Familial Defective ApoB100	↑↑ LDL	1:100	↓ApoB100 binding to LDLR
Polygenic Hypercholesterolemia	↑ Chol	Common	unknown
Primary Hypertriglyceridemia			
Familial Hypertriglyceridemia	↑TG ↓HDL ↑VLDL	Common	↓VLDL breakdown ↑ VLDL synthesis
Mixed Hyperlipidemia			
Familial Combined Hyperlipidemia	↑LDL↑TG ↓ HDL	1:100	Unknown, dominant inheritance
Disorders of HDL metabolism			
Polygenic low HDL	↓ HDL	Common	Obesity, diabetes high carb diets
Familial hypoalphalipoproteinemia	↓ HDL	1:100	Unknown, dominant inheritance

Genetic Causes of Dyslipidemia

- Familial Combined Hyperlipidemia
  - Increased TC, LDL and/or triglycerides; decreased HDL
  - Most common genetic dyslipidemia: prevalence 1:50
  - Heterogenous inheritance
  - Accounts for 10-20% of patients with premature CAD
- Defects in HDL Metabolism
  - Most often low HDL is secondary to other dyslipidemia
  - Not all associated with increased CAD risk (e.g. apo AI_{Milano})
  - Tangier's Disease
  - CETP defects result in increased HDL

Secondary Causes Of Dyslipidemias

Causes of Hyperlipidemia

- Diet
- Hypothyroidism
- Nephrotic syndrome
- Anorexia nervosa
- Obstructive liver disease
- Obesity
- Diabetes mellitus
- Pregnancy
- Obstructive liver disease
- Acute hepatitis
- Systemic lupus erythematousus
- AIDS (protease inhibitors)

Secondary Causes of High TG

Lifestyle

- Physical inactivity
- High CHO intake (>60%)
- Excessive alcohol
- Obesity

Medications

- ERT / OCP / Tamoxifen
- Steroids / immunosuppressants
- Beta blocker / thiazides
- Retinoids
- Protease inhibitors (HIV)
- Atypical anti-psychotics

Diseases

- Metabolic syndrome
- Diabetes (type 2)
- Nephrotic syndrome
- Chronic kidney disease
- Cushing syndrome
- Hypothyroidism
- Pregnancy

Dunbar and Rader. CCJM 2005;72:661-680

Types of Hyperlipoproteinemias

Fredrickson Classification of Hyperlipoproteinemia

Type I Hyperlipoproteinemia	Lipoprotein Lipase Deficiency Increased Chylomicrons and VLDL Hypertriglyceridemia
Type II a Hyperlipoproteinemia	Defect in LDL Receptors Increased LDL levels in blood Hyperbetalipoproteinemia Hypercholesterolemia
Type II b Hyperlipoproteinemia	Increased production of Apo B Increased production of VLDL and impaired LDL catabolism Increased VLDL and

Type III
Familial Dysbeta Lipoproteinemias

Defect in ApoE
Broad Beta Disease
Increased IDL

Type IV
Hyper-pre-β-Lipoproteinemia

Impaired VLDL metabo

Increased VLDL

Due to acquired conditi

- ❑ **Obesity**
- ❑ **Alcoholism**
- ❑ **Diabetes mellitus**

Type V
Combined Hyperlipoproteinemia

Increased VLDL and Chylomicrons
Due to acquired conditions viz

- ❑ **Obesity**
- ❑ **Alcoholism**
- ❑ **Diabetes mellitus**

Fredrickson Classification of the Hyperlipidemias

Phenotype	Lipoprotein(s) elevated	Serum cholesterol concentration	Serum triglyceride concentration	Relative frequency, %
I	Chylomicrons	Normal to ↑	↑↑↑↑	<1
IIa	LDL	↑↑	Normal	10
IIb	LDL and VLDL	↑↑	↑↑	40
III	IDL	↑↑	↑↑↑	<1
IV	VLDL	Normal to ↑	↑↑	45
V	VLDL and chylomicrons	↑ to ↑↑	↑↑↑↑	5

Deficiency Of Lipoprotein Lipase Leads To **Familial Type I Hyperlipoproteinemia**

- **Defect in Lipoprotein Lipase** activity
- **Does not clear circulating Chylomicrons and VLDL**;
- **Increases levels of circulating Chylomicrons and VLDL**
- Associated **Hypertriglyceridemia**
- This is termed as **Familial Type I Hyperlipoproteinemia.**

Type I Hyperlipoproteinemias

- **Shows a dramatic accumulation (≥1000 mg/dl) of Chylomicrons and VLDL in plasma**

- Usually associated with acute abdomen pain due to acute pancreatitis

- ↑ plasma TAG even in the fasted state

Type III Hyperlipoproteinemia

- Familial dysbetalipoproteinemia
- Due to Apo E deficiency
- Associated with Hypercholesterolemia & premature Atherosclerosis

Hypolipoproteinemias

Hypolipoproteinemias

- Hypolipoproteinemias are abnormal conditions
- With **decreased levels of circulating Lipoproteins in blood.**

Conditions Of Hypolipoproteinemias

- **Decreased synthesis of Lipoproteins**
- **Deficiency of Lipotropic factors** required for Lipoprotein biosynthesis.

Types Of Hypolipoproteinemias

Familial Hypobetalipoproteinemia

- **Impairment in synthesis of Apo B**
- Characterized with **low LDL levels.**

Abeta Lipoproteinemia

- Rare disorder
- **No synthesis of Apo B (Total Absence)**
- **Absence of LDL** (Beta Lipoprotein) in blood circulation
- **Defect in TAG-transfer protein**
- **Accumulation of TAG in liver**

Familial Alpha Lipoprotein Deficiency

Tangiers Disease

- **Absence of HDL (Alpha Lipoprotein) in blood**
- **Affects severely Reverse transport of Cholesterol**
- Hypercholesterolemia
- Increased risk of Atherosclerosis and its Complications.

Combined Hyperlipoproteinemia

- Presence of elevated levels **of both serum Total Cholesterol and Triacylglycerols.**
- Genetic form of this condition
  - Familial Combined Hyperlipoproteinemia (FCH)
  - **Type V Hyperlipoproteinemia**
    - An accumulation of Cholesterol-rich VLDL and Chylomicron remnants as a result of defective catabolism of those particles

Diagnosis And Therapeutic Strategy Of Dyslipidemias

A. Identify patients at risk

1. Routine screening of Serum Lipid profile
2. Assessment of contributing risk factors

B. Non-Pharmacologic therapy

1. Diet modification
2. Lifestyle modification

C. Pharmacologic therapy

- Lipids and lipoproteins are important indicators of CHD risk,

- This is major reason for their measurement in research, as well as in clinical practice.

Lipid Profile and Lipoprotein Analyses

Estimation Of Lipid Profile

- Serum Triacylglycerol
- Serum Total Cholesterol
- Serum VLDL
- Serum LDL Cholesterol
- Serum HDL Cholesterol

Hypertriglyceridemia

- **Serum Triacylglycerol**
  - Borderline = 150-200 mg/ dl
  - High 200-500 mg/dl
  - Very High > 500 mg/dl
- **Familial Hypertriglyceridemia**
  - Genetic
- **Secondary Hypertriglyceridemia**
  - Hormonal imbalances
  - Imbalance between synthesis and clearance of VLDL

Hypertriglyceridemia

- Generally caused by deficiency of LPL or LPL cofactor.
- LPL hydrolyzes TAG in Chylomicrons and VLDL
- Deficiency of LPL prevents processing and clearing of Lipoproteins.
- Elevated even with fasting condition.

Hypercholesterolemia

- **Familial Hypercholesterolemia (FH)**
  - –Homozygous rare 1/million
    - Total cholesterol 800-1000 mg/dl
    - Heart attack as early as teenage years
  - –Heterozygous cholesterols 300-600 mg/dl
    - Heart attacks 20-50 years

Hypercholesterolemia

- **Familial hypercholesterolemia (FH)**
  - Primarily LDL elevations
  - Synthesis is normal but decrease or lack LDL receptors
  - Therefore LDL builds-up in serum
  - Since cells cannot acquire from LDL increase internal synthesis

LDL Methods

- **Friedewald Calculation**
  - VLDL is estimated as TAG/5

LDL = Total Cholesterol – HDL – TAG/5

Lipoprotein Assay Methods

- **Separate Lipoprotein Fractions By:**

– Electrophoresis – Agarose or Polyacrylamide
– Chromatographic
– Precipitation
– Ultracentrifugation
– Immunochemical

Serum Triglycerides

Normal

- Less than 150 mg/dL

Borderline High

- 150-199 mg/dL

High

- 200-499 mg/dL

Very High

- 500+ mg/dL

Serum Total Cholesterol

Normal

- Less than 200 mg/dL

Borderline High

- 200-239 mg/dL

High

- 240 mg/dL or higher

HDL Cholesterol

Optimal:

- 60+ mg/dL for both males and females

At Risk for Heart Disease:

- Women: less than 50 mg/dL
- Men: less than 40 mg/dL

LDL Cholesterol

Optimal

- Less than 100 mg/dL

Near or above Optimal

- 100-129 mg/dL

Borderline High

- 130-159 mg/dL

High

- 160-189 mg/dL

Very High

- 190+ mg/dL

–Cholesterol Levels of:

–Healthy person = < 200 mg/dl

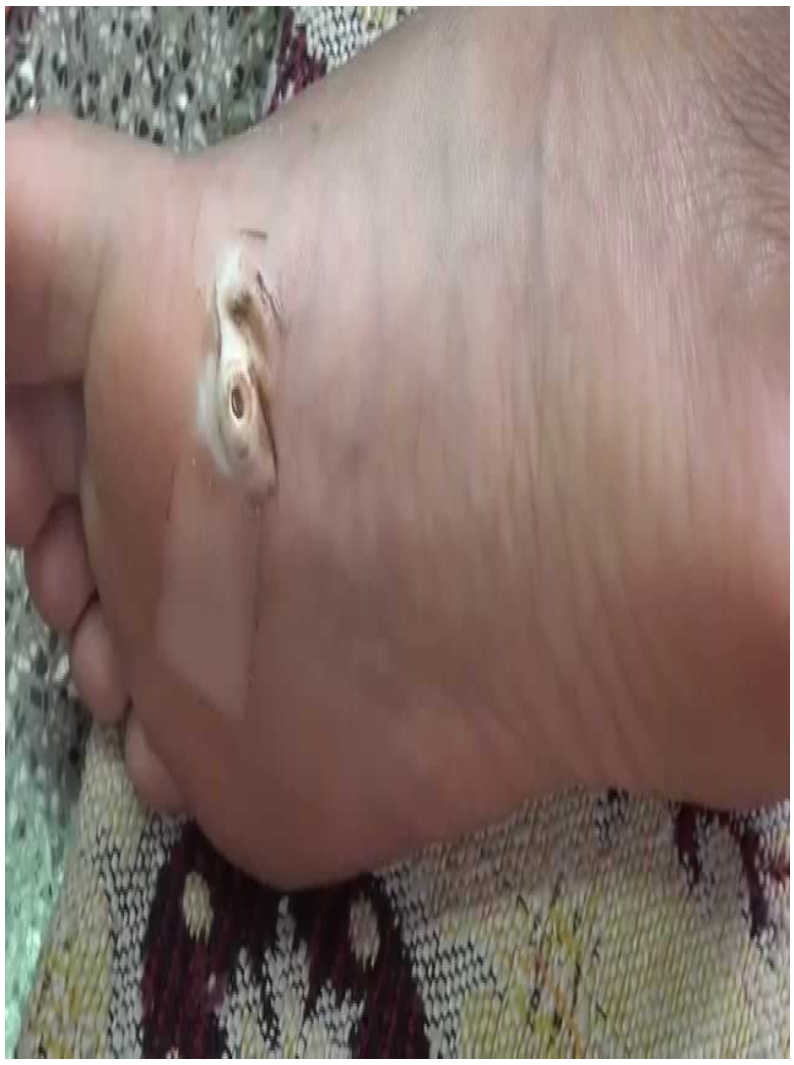
–Heterozygous individuals = 300 mg/dl

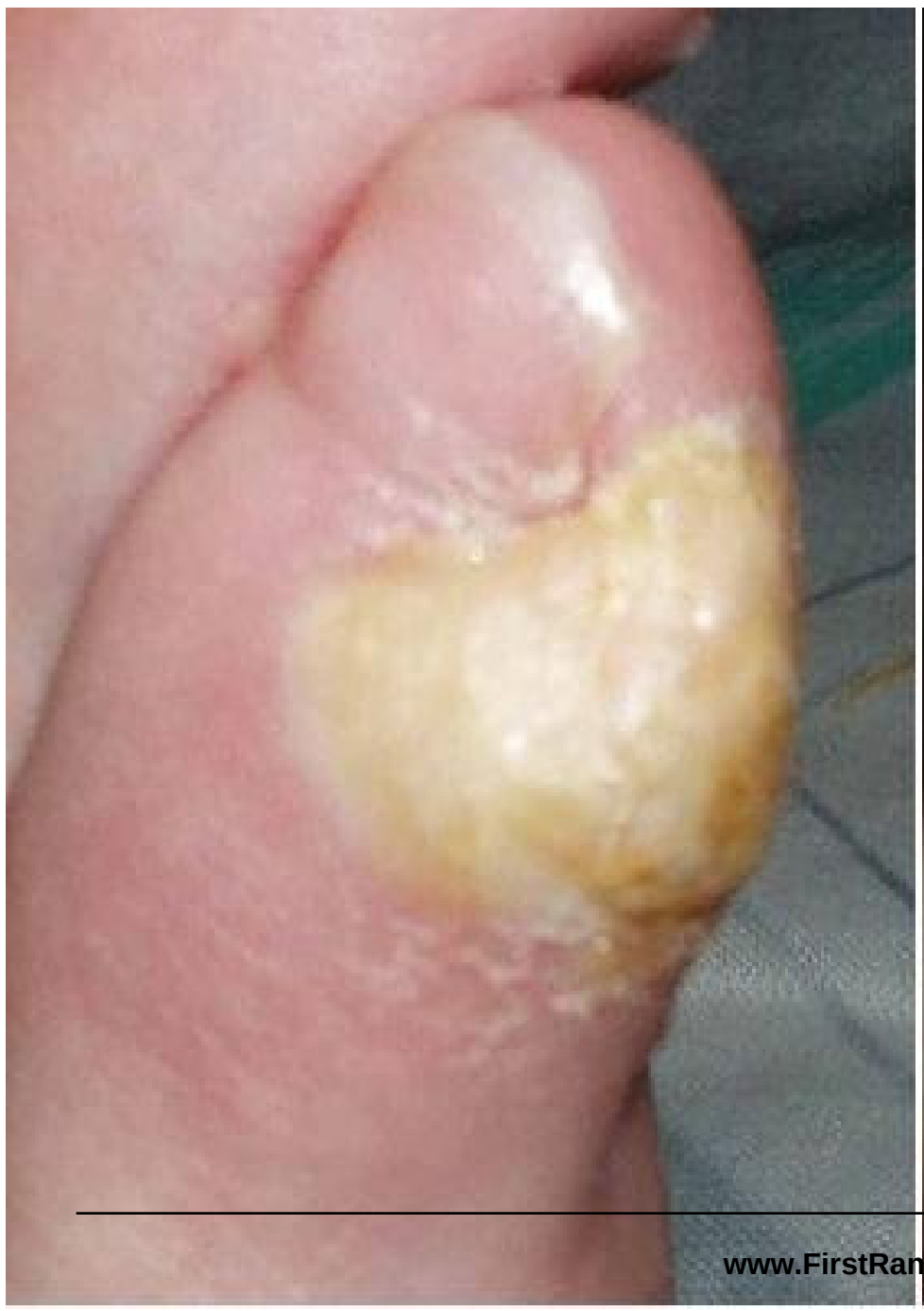
–Homozygous individuals = 680 mg/dl

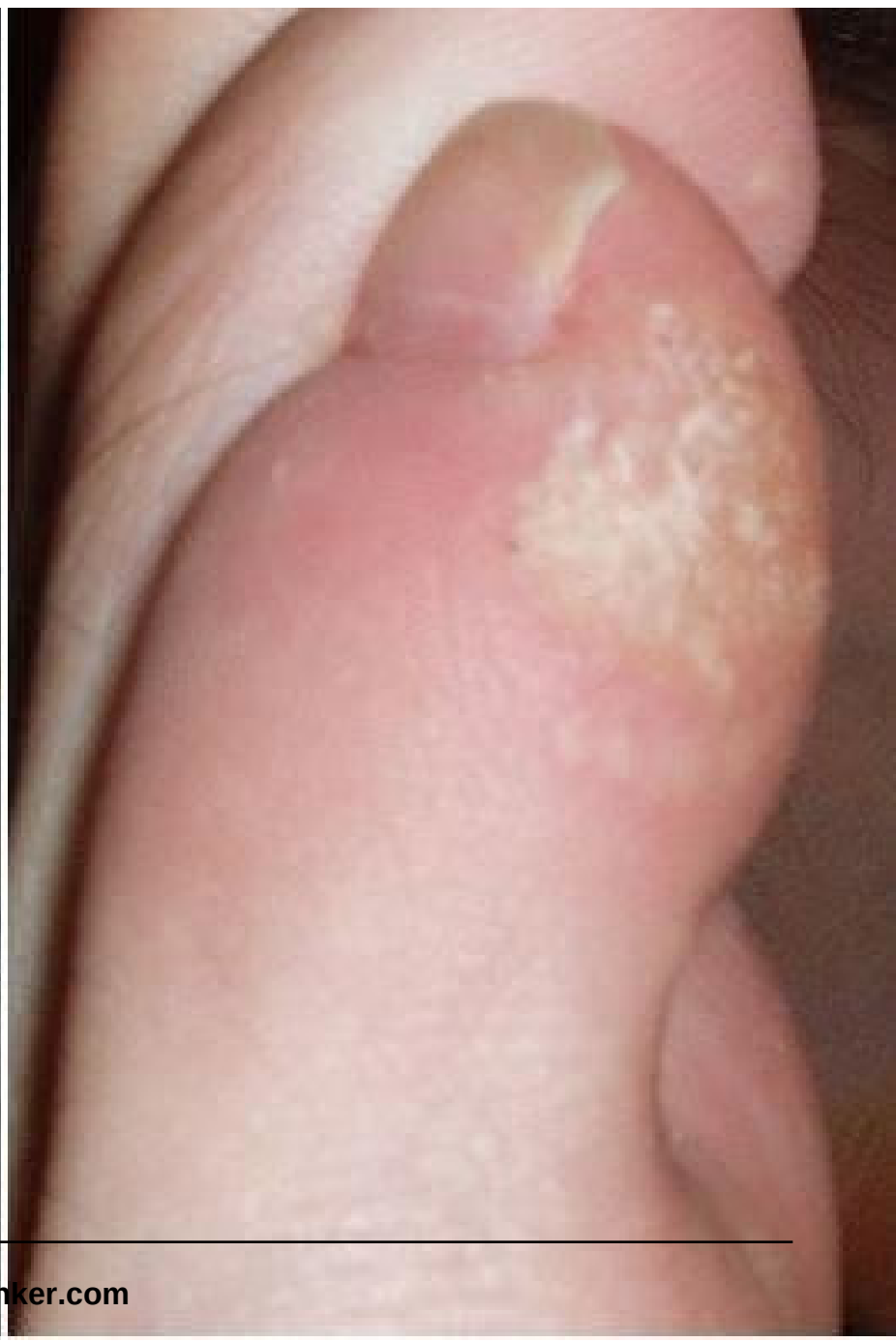
Consequences Of Dyslipoprotein Metabolism

- Fish Eye Disease
- Fatty Liver
- Atherosclerosis and its Complications

Fish Eye Disease







Fatty Liver

Role Of Liver In Lipid Metabolism

- **Liver is the Biochemical Factory of Human Body.**
- Liver plays an **important role in Lipid metabolism.**
- Major **pathways of Lipid metabolism are efficiently carried out in Liver.**

Lipid Metabolism
At Liver
In Well Fed Condition

- Liver in well fed condition efficiently carries out various metabolic pathways of Lipid Metabolism.
  - **De Novo biosynthesis of Fatty acids**
  - **Triacylglycerol Biosynthesis**
  - **Cholesterol Biosynthesis**
  - **Phospholipid Biosynthesis**
  - **Glycolipid Biosynthesis**
  - **VLDL Biosynthesis**

Lipid Metabolism
At Liver
In Emergency Condition

- **Liver in emergency condition** carries following metabolic pathways of Lipid metabolism efficiently:
  - **Beta Oxidation of Fatty acids**
  - **Ketogenesis**
  - **Bile Acid and Bile Salt** Formation

- Though **Liver is predominant site for Lipid biosynthesis.**

- **Liver is not the storage organ for Lipids.**

- Normally **3-5% of Lipids are present in Hepatocytes.**

- **Endogenously biosynthesized Lipids in Liver are**

- Mobilized out in the **form of VLDL molecule.**

- **Efficient formation of VLDL in Liver**
- **Does not allow the excess of Lipids to remain in Liver tissue.**

Fatty Liver/ Fatty Liver Disease/ Hepatosteatosis

What Is Fatty Liver?

- **Fatty Liver** is **an abnormal condition**

- Where there is **more than 5% of Lipids retained in Hepatocytes.**

What Is Fatty Liver Disease?

- **Fatty Liver disease** (**FLD**), is a **reversible condition of Liver**
- Wherein **large vacuoles of Lipids accumulate in Liver cells**
- Via the process of **Steatosis** (Abnormal retention of Lipids within a cell)

What Is Steatohepatitis ?

- Progressive inflammation of Liver (Hepatitis),
- Due to abnormal accumulation of Lipids(Steatosis) **is termed as Hepatosteatosis/Steatohepatitis**

.

Causes Of Fatty Liver

Clinical Conditions Leading To Fatty Liver

OR

Risks For Developing Fatty Liver

- **Defect in Hepatic**
  - –Biosynthesis of Lipids
  - –No Mobilization of Endogenously biosynthesized Lipids in Liver
- **Accumulates Lipids in Liver**

- **Increased biosynthesis of Lipids** than the mobilization capacity ,**due to increased Carbohydrates.**

- **Decreased mobilization of Lipids from Liver** cells **due to decreased VLDL formation.**

- Deficiency of **Lipotropic factors affects**
- The **VLDL formation** and **mobilization of Lipids out** of Hepatocytes.

Conditions Leading To Fatty Liver

- **Metabolic Syndrome**
  - **Obesity**
  - **Hypertension**
  - **Dyslipidemias**
  - **Diabetes mellitus**
- **Alcoholism**
- **Malnutrition**

(Deficiency of Lipotropic Factors)

- **Wilsons Disease**
- **Hepatitis A**
- **Hepatitis C**
- **Hepatotoxic Drugs** : MTX, VA, Acetaminophen, TC, Tamoxifen, Nefidepine, Amiodarone, CCl_4 etc

Lipotropic Factors and Their Role

Adequate Presence of Lipotropic factor

Prevents Retention of Lipids in Liver

There by preventing Fatty Liver.

- **Lipotropic Factors** are chemical **substances which helps in formation of Phospholipids**.

- This in turn helps in **proper formation and mobilization of VLDL out from Liver.**

Names Of Lipotropic Factors

- Lipotropic Factors are chemicals involved in biosynthesis of Phospholipids:
  - **Choline**
  - **Betaine forms Choline**
  - **Inositol**

Amino Acids As Lipotropic Agents

- **Glycine**
- **Serine**
- **Methionine**

Vitamins As Lipotropic Factors

- Vitamin B 12
- Folic Acid

Types Of Fatty Liver

4 Types Of Fatty Liver

- Alcoholic Fatty Liver
- Non Alcoholic Fatty Liver Disease (NAFLD)
- Non Alcoholic Steatohepatitis (NASH)
- Acute Fatty Liver of Pregnancy

Consequences Of Fatty Liver

- Fatty liver is a **reversible condition** and **usually goes away on its own.**

- Generally Fatty liver **often has no symptoms** and

- **Does not cause any permanent damage.**

Consequences Of Fatty Liver

- **Constant accumulation** of **abnormal excess amount of Lipids in Hepatocytes**
- **Affects the normal Liver functions**
- **Leads to Parenchymal damage to Liver Tissues**
- **Causes Liver Cirrhosis.**

- Excess of Lipids deposition in Hepatocytes
- **Interferes the biochemical functions**
- Brings inflammation of Liver **(Hepatitis)**
- **Changes the cytological features**
- Damages the cell components
- Causes Liver **Fibrosis**
- Leads to Liver **Cirrhosis**
- Liver **Carcinoma**

Natural History of Fatty Liver Disease

Fatty liver

↓

Steatohepatitis

↓

Steatohepatitis + Fibrosis (First Stage of Scar)

↓

Steatohepatitis + Cirrhosis

↓

Cryptogenic Cirrhosis

When there is repeated damage to the Liver

Permanent scarring of Hepatocytes takes place

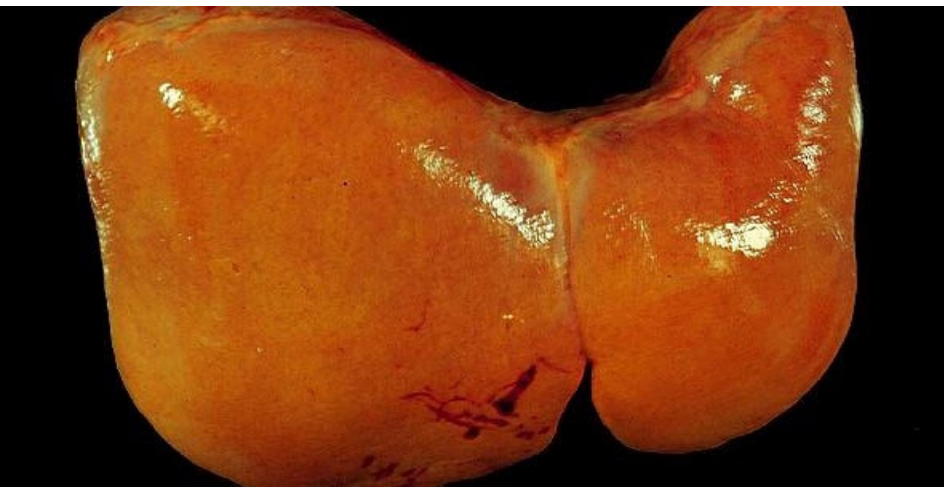
This is called Liver Cirrhosis

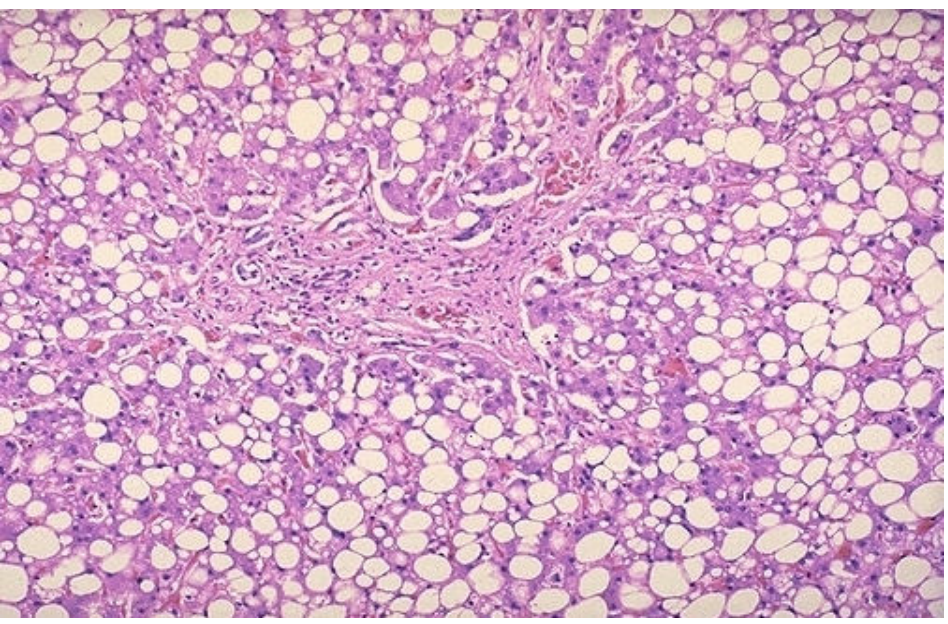
Diagnostic Features OF Fatty Liver Disease

Laboratory Abnormalities In Fatty Liver Disease

- 2 - 4 fold ↑ ALT & AST
- AST: ALT Ratio < 1
- ALP slight ↑ in 1/3
- Dyslipidemia - ↑ TAG
- FBG and PPBG ↑
- BUN & Creatinine - N
- Normal Albumin. PT
- Low ANA + < 1 in 320
- ↑ Serum Ferritin
- ↑ Iron saturation
- AST: ALT Ratio > 1 if Cirrhosis sets in

Fatty liver





Normal liver