
بسم الله الرحمن الرحیم

# Disorders of lipid profile in clinical laboratory

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**PhD in clinical biochemistry**

# Outline

- Dyslipidemia (classic hyperlipidemia classification)
- Hypertyglyceridemia
- Hyper cholestrolemia
- NAFLD
- CAD

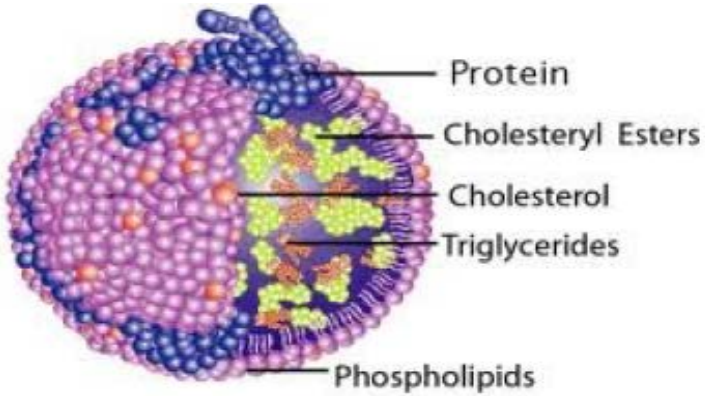
# What Is Driving The Dual Epidemic?

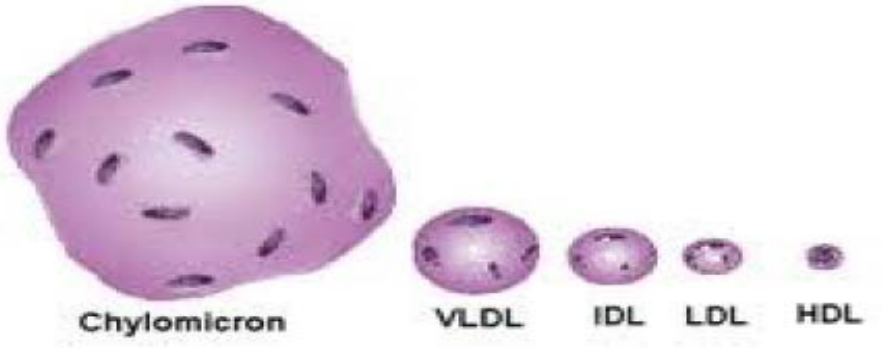




Changes in our lifestyle!

# Lipoproteins- Structure, classification



# Classic hyperlipidemia classification

TABLE 17-3

Classic Hyperlipidemia Phenotypes

| WHO ICD and OMIM Numbers | Type | Particle | Triglycerides | Cholesterol | Comments |
|---|---|---|---|---|---|
| E78.3<br>238600 | 1 (familial chylomicronemia or LPL deficiency) | CM | High | Normal | Low cardiac risk; hereditary, found mostly in pediatric patients and young adults; autosomal recessive mutation in *LPL* or *APOC2; APOA5, LMF-1,* and *GPIHBP1* mutations are linked to this phenotype. |
| E78.0<br>143890 | 2A (heterozygous and homozygous familial hypercholesterolemia) | LDL | Normal | High | High cardiac risk; mostly polygenic disease; about 10% are monogenic; heterozygous form is due to mutations in *LDLR, APOB,* or *PCSK9*; homozygous form is due to mutations in *LDLR* or *LDLRAP1* (ARH). |
| E78.4<br>144250 | 2B (combined hyperlipoproteinemia) | VLDL, LDL | High | High | High cardiac risk; polygenic disease; links to mutations in *USF1, APOB,* and *LPL* |
| E78.2<br>107741 | 3 (dysbetalipoproteinemia) | IDL | High | High | High cardiac risk; mutations in *APOE* gene or homozygous for E2 allele of *APOE* |
| E78.1<br>144600, 145750 | 4 (primary hypertriglyceridemia) | VLDL | High | Normal | Lower cardiac risk than type 2 or 3; polygenic disease |
| E78.3<br>144650 | 5 (mixed hyperlipidemia) | VLDL, CM | High | High | Low cardiac risk; polygenic disease; 10% of patients have mutations in *LPL, APOC2,* and *APOA5*; mutations in *APOE, TRIB1, CHREBP, GALNT2, GCKR,* and *ANGPTL3* are thought to contribute to this disease. |

*ANGPTL3,* Angiopoietin-like 3; *APOA5,* apolipoprotein A-V; *APOB,* apolipoprotein B; *APOC2,* apolipoprotein C-II; *APOE,* apolipoprotein E; *CHREBP,* carbohydrate response element binding protein (or *MLXIPL*); *CM,* chylomicron; *GALNT2,* UDP-N′-acetyl-alpha-D-galactosamine-polypeptide *N*-acetylgalactosaminyltransferase 2; *GCKR,* glucokinase regulator; *ICD,* International Classification of Diseases; *IDL,* intermediate-density lipoprotein; *LDL,* low-density lipoprotein; *LDLRAP1,* LDLR adaptor protein 1 (also known as ARH); *OMIM,* Online Mendelian Inheritance in Man; *TRIB1,* tribbles homologue 1; *USF1,* upstream transcription factor 1; *VLDL,* very-low-density lipoprotein; *WHO,* World Health Organization.

# Classic hyperlipidemia classification

TABLE 17-11

**Pertinent Details of the Fredrickson Classification**

| Type | Refrigerator Test | Gel Electrophoresis | Clinical Presentation |
|---|---|---|---|
| 1 | Positive; clear plasma | Normal | Eruptive xanthoma; acute, recurrent pancreatitis in early childhood; lipids improve on low-fat diet |
| 2a | Negative; clear plasma | Increased β band | Xanthelasma, tendon xanthoma; premature coronary disease; autosomal dominant familial inheritance; commonly known as familial hypercholesterolemia |
| 2b | Negative; cloudy plasma; increased β and pre-β band | Isolated xanthelasma may be present; premature coronary disease; autosomal dominant pattern; affected family members must have varied patterns (e.g., isolated hypertriglyceridemia, isolated hypercholesterolemia, combined hyperlipidemia) to meet diagnostic criteria for familial combined hyperlipidemia | |
| 3 | Occasional cloudy plasma; increased pre-β band; eruptive xanthoma and palmar xanthoma; premature coronary disease; autosomal recessive pattern; a secondary cause of dyslipidemia, such as hypothyroidism, can unmask type 3, and treatment of the secondary condition can return lipids to normal | | |
| 4 | Negative; cloudy plasma; increased $\alpha_2$ band | May or may not be associated with premature coronary disease | |
| 5 | Positive; cloudy plasma; increased $\alpha_2$ band | Eruptive xanthoma; may be associated with pancreatitis; may be associated with premature coronary disease | |

# Enzyme in lipid metabolism

**TABLE 17-6**
**Enzymes and Other Proteins Important for Lipoprotein Metabolism**

| Enzyme | Gene Location | Function | Deficiency | Tissue Expression |
|---|---|---|---|---|
| ABCG5 | 2p21 | Forms heterodimers with ABCG8 to pump out plant sterols back into the intestinal lumen | Increased plant sterol levels in plasma that can disrupt cell membranes and cause sitosterolemia; influences cholesterol levels in plasma | Tissue expression in liver, colon, and intestines |
| ABCG8 | 2p21 | Forms heterodimers with ABCG5 to pump out plant sterols back into intestinal lumen; also associated with cholesterol and sterol excretion in bile | Increased plant sterol levels in plasma that can disrupt cell membranes and cause sitosterolemia; influences cholesterol levels in plasma | Tissue expression in the liver, intestines, and gallbladder |
| ABCA1 | 9q22-31 | Efflux of cholesterol from peripheral cells into HDL | Tangier disease, with very low HDL and accumulation of lipids in peripheral cells | Many cell types, prominently in the liver, testis, and adrenal |
| CETP | 16q21 | Transfers CE, PL, and TG among lipoproteins, esp. the transfer of CE from HDL to apoB-100–containing lipoproteins in exchange for TG | Deficiency results in large cholesterol-laden HDL | Produced in liver and circulates with HDL |
| EL | 18q21.1 | Hydrolysis of PL and TG in lipoproteins, esp. PL in HDL. Homologous to LPL and EL and pancreatic lipase | Increased levels of $HDL_2$ and large buoyant LDL. Overexpression in mice, decreased TC, PL, and HDL-C | Expressed in many tissues, including liver. Synthesized by endothelium |
| HL | 15q22-23 | Hydrolysis of TG and PL, esp. from $HDL_2$ and may be necessary for HDL metabolism. Also active on lipids in VLDL remnants and IDL. Not very active on newly released VLDL or CM | Increased TC, TG, and HDL-C in deficiency | Associates with nonparenchymal liver cells |
| LCAT | 16q22.1 | Catalyzes the esterification of cholesterol, esp. in HDL, by promoting transfer of fatty acids from lecithin to cholesterol. Enables HDL to accumulate cholesterol as CE. Activated by apoA-I | Deficiency results in decreased HDL. | Produced in liver and circulates with HDL |
| LPL | 8q22 | Hydrolysis of TG in lipoproteins (esp. VLDL and CM), releasing free fatty acids and glycerol to tissues. ApoC-II are essential cofactors. | Large CM and VLDL with very high TG levels | Present on surface of capillary endothelial cells in adipose tissue and skeletal and heart muscle, but not produced by endothelial cells |
| LDLR | 19p13.2 | Binds apoE and apoB-100 and mediates endocytosis of lipoproteins, mostly LDL, but also VLDL, IDL, and CM remnants | Familial hypercholesterolemia results primarily in elevated LDL | Expressed on most cell types, but hepatic receptors clear 70% of LDL |
| MTP | 4q24 | Lipidates and regulates secretion of ApoB particles from the liver and intestines | Deficiency of MTP function leads to abetalipoproteinemia where ApoB lipoproteins are virtually undetectable in plasma. | Expression is seen in liver, intestines, heart, kidney, and eye |
| PLTP | 20q12 | Transfer of PL to and from HDL. Important for HDL growth and remodeling | Deficiency in mice results in low HDL. | Expressed on many cell types |
| PCSK9 | 1p32.3 | Influences the number of LDLRs expressed on cell surface | Depending on mutation—either gain of function or loss of function—the presence of PCSK9 affects availability of LDLR on cell surface and, consequently, the levels of LDL in plasma; gain of function leads to more LDL in plasma; loss of function associates with increased LDLR expression and thus less LDL in plasma. | Secreted protein by the liver cells; expressed in pancreatic islet beta cells and neuronal cells |
| SR-B1 | 12q24.31 | Binds HDL on cell surface. Plays a role in selective uptake of CE from HDL in liver and steroidogenic tissues. May also enable macrophages to | Accumulation of large CE-rich HDL, and accelerated atherosclerosis in mice | Macrophage, adrenal, liver and testis |

# HYPERTRIGLYCERIDEMIA

- **Triglyceride levels are classified as**
  - Normal (<150 mg/dL),
  - Borderline high (150-199 mg/dL)
  - High (200-499 mg/dL)
  - Very high (≥500 mg/dL)
- Causes of very high triglycerides
  - Genetic disorders (LPL deficiency, apolipoprotein C-II deficiency, apolipoprotein A-V deficiency, GPIHBP1 deficiency, Marinesco-Sjogren syndrome, familial hypertriglyceridemia);
  - Acquired disorders of the metabolism (hypothyroidism, pregnancy, poorly controlled insulinopenic diabetes)
  - Drugs (α-interferon, atypical antipsychotics, …
  - Diet (alcohol excess, especially with a high–saturated fat diet);
  - Diseases (autoimmune chylomicronemia [e.g., antibodies to LPL, SLE], chronic idiopathic urticaria, renal disease).

# HIGH TRIGLYCERIDES WITH NORMAL CHOLESTEROL

- Diabetic Dyslipidemia
- Familial Hypertriglyceridemia
- Lipoprotein Lipase Deficiency
  (Hyperlipoproteinemia Type 1 or Hyperchylomicronemia)
- ApoC-II Deficiency
- ApoC-III Excess
- ApoA-V

# Hypercholesterolemia

- **HIGH CHOLESTEROL IN CHILDREN**
  - Selective screening (starting at 2 years of age) of children and adolescents with a family history of remature cardiovascular disease or those with at least one parent with high blood cholesterol

TABLE 17-10

Classification of Total and LDL-Cholesterol in Children: Targeted Fasting Screen in Children over Age 2 with Family History of Dyslipidemia or Premature CHD

| Category | Total Cholesterol (mg/dL) | LDL-Cholesterol (mg/dL) |
|---|---|---|
| Acceptable | <170 | <110 |
| Borderline | 171-199 | 111-129 |
| High | ≥200 | ≥130 |

# Hypercholesterolemia (Cont.)

- **HIGH CHOLESTEROL WITH HIGH LDL-C**
- These disorders share hyperbetalipoproteinemia (Fredrickson Type 2A)
  - Polygenic (Nonfamilial) Hypercholesterolemia
  - Familial Hypercholesterolemia (LDLR gene mutations (deletion, missense, nonsense, and insertion)
  - Familial Defective ApoB
  - Sitosterolemia (phytosterols accumulate in plasma, mutations in the *ABCG8* or *ABCG5* gene, chromosome 2p21)
  - Autosomal Recessive Hypercholesterolemia (ARH)
  - Autosomal Dominant Hypercholesterolemia (ADH)

# Hypercholesterolemia (Cont.)

- **HIGH CHOLESTEROL WITH HIGH TG**
  - Familial Combined Hyperlipidemia (Type 2B)
  - Acquired Combined Hyperlipidemia
  - Dysbetalipoproteinemia (Type 3)
  - Hepatic Lipase Deficiency
  - Cholesterol 7-Alpha-Hydroxylase Deficiency

# LOW TOTAL CHOLESTEROL AND TRIGLYCERIDE

- Abetalipoproteinemia
- Hypobetalipoproteinemia
- Chylomicron Retention Disease (Anderson's disease)
  - presents in childhood with fat malabsorption disorder is linked to the *SARA2* gene on chromosome 5q3 that encodes the Sar1 GTPase protein.

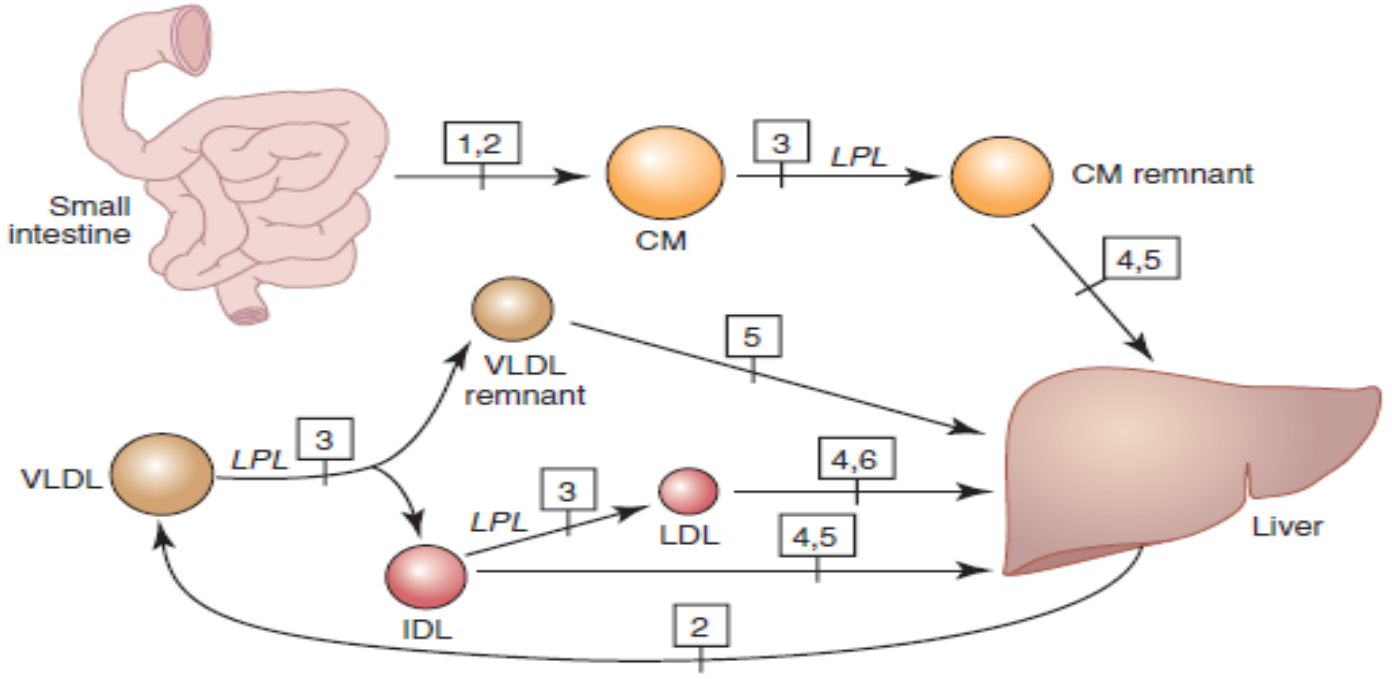
# ISOLATED LOW HDL-C

- Familial Hypoalphalipoproteinemia
- ApoA-I Deficiency and ApoC-III Deficiency
- ApoA-I Variants
- Tangier Disease
- Lecithin : Cholesterol Acyltransferase Deficiency

# ISOLATED HIGH HDL-C

- Cholesteryl Ester Transfer Protein Gene Defects
  - CETP, the plasma protein that facilitates the transfer of cholesteryl esters from HDL to apoB-100–rich proteins (VLDL and LDL) in exchange for triglycerides.
  - CETP deficiency is an autosomal recessive disorder.
  - HDL particles are large and laden with cholesterol ester, and apoA-I is increased,

# Review of dyslipidemia




1 - Chylomicron retention (Apo B-48 defect)
2 - Hypobetalipoproteinemia/Abetalipoproteinemia
3 - LPL deficiency/Apo C II deficiency
4 - Familial hypercholesterolemia
5 - Dysbetalipoproteinemia (Type III hyperlipoproteinemia, associated with Apo-E-2)
6 - Familial defective Apo B

**Figure 17-5 Disorders associated with the transport of lipids.** *Apo,* Apolipoprotein; *CM,* chylomicron; *IDL,* intermediate-density lipoprotein; *LPL,* lipoprotein lipase; *VLDL,* very-low-density lipoprotein.

# Review of dyslipidemia

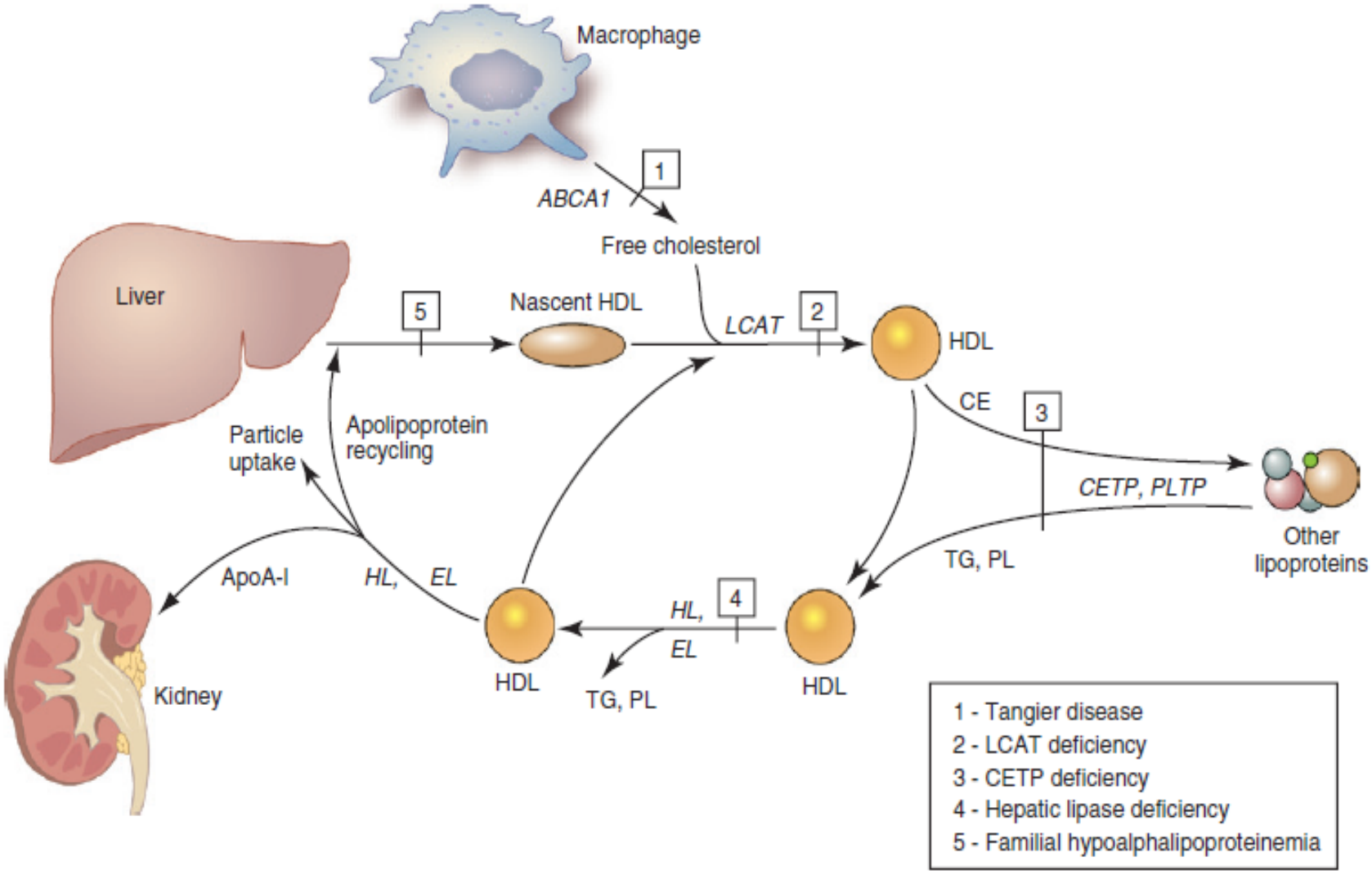


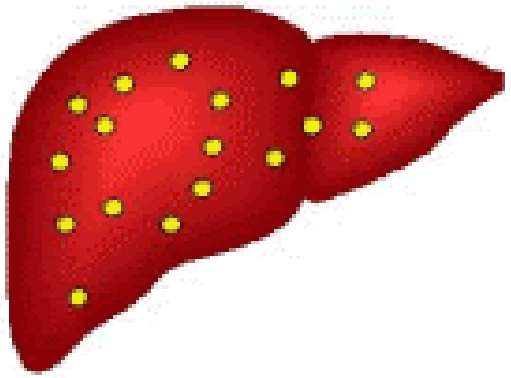

**Figure 17-6** **Disorders associated with the reverse transport of lipids.** *ABCA1*, Adenosine triphosphate (ATP)-binding cassette protein A-1; *Apo*, apolipoprotein; *CE*, cholesterol ester; *CETP*, cholesterol ester transfer protein; *EL*, endothelial lipase; *HDL*, high-density lipoprotein; *HL*, hepatic lipase; *LCAT*, lecithin:cholesterol acyltransferase; *PL*, phospholipids; *PLTP*, phospholipid transfer protein; *TG*, triglycerides.

# Clinical feature of lipoprotein metabolism

- **1. Fatty Liver**
- is an abnormal accumulation of certain fats (triglycerides) inside liver cells.
- Hepatic triacylglycerol synthesis provides the immediate stimulus for the formation and secretion of VLDL.
- Impaired VLDL formation or secretion leads to no mobilization of lipid components from the liver, results in fatty liver.

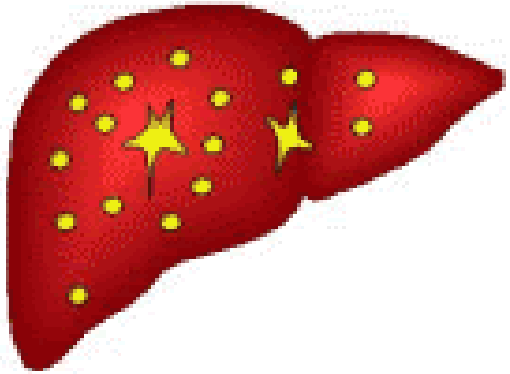
# The Spectrum of NAFLD

## Fatty Liver



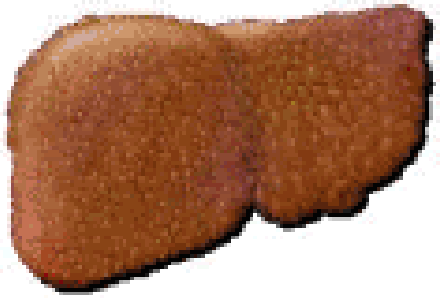
Fat accumulates in the liver

## NASH

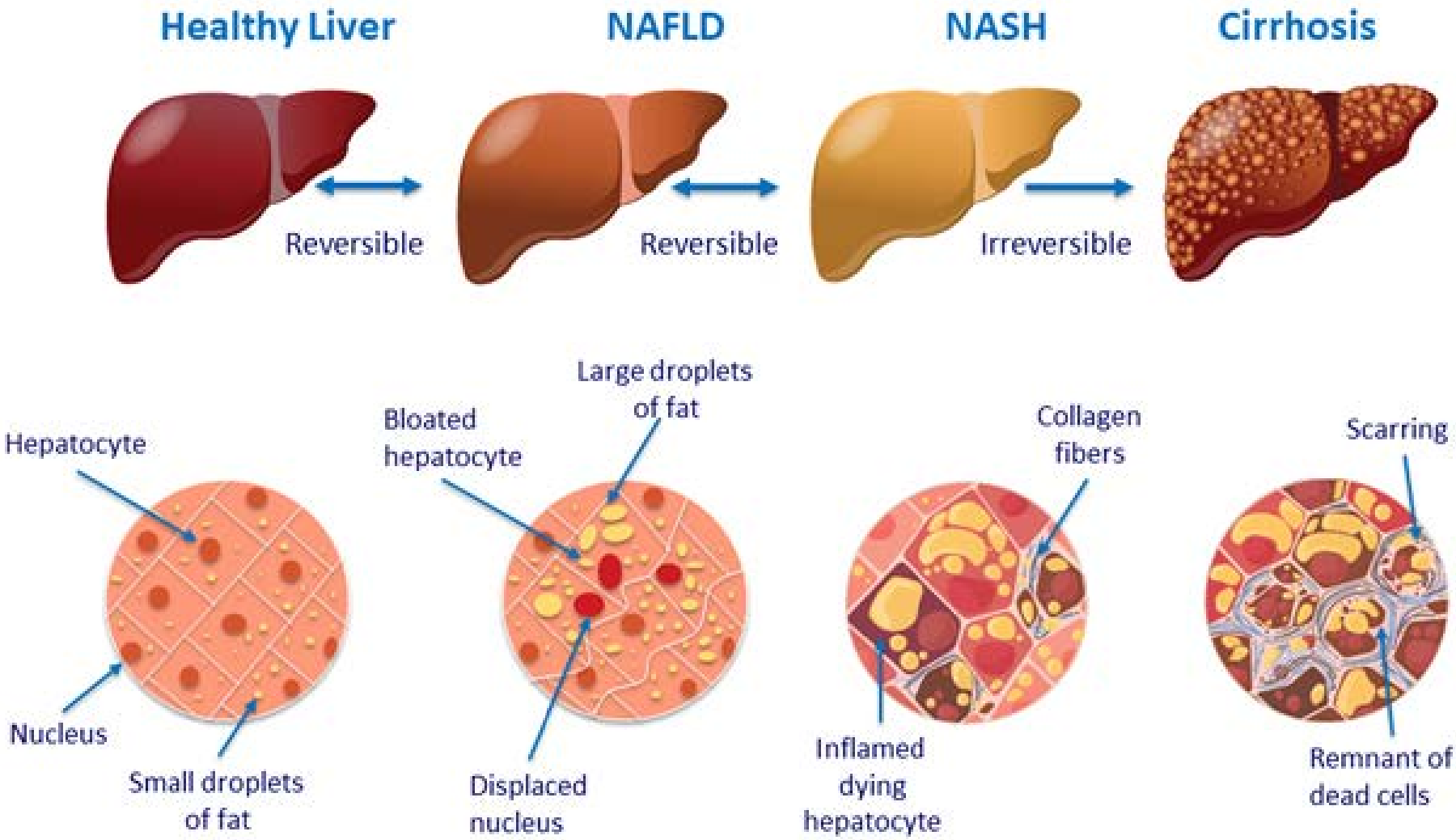


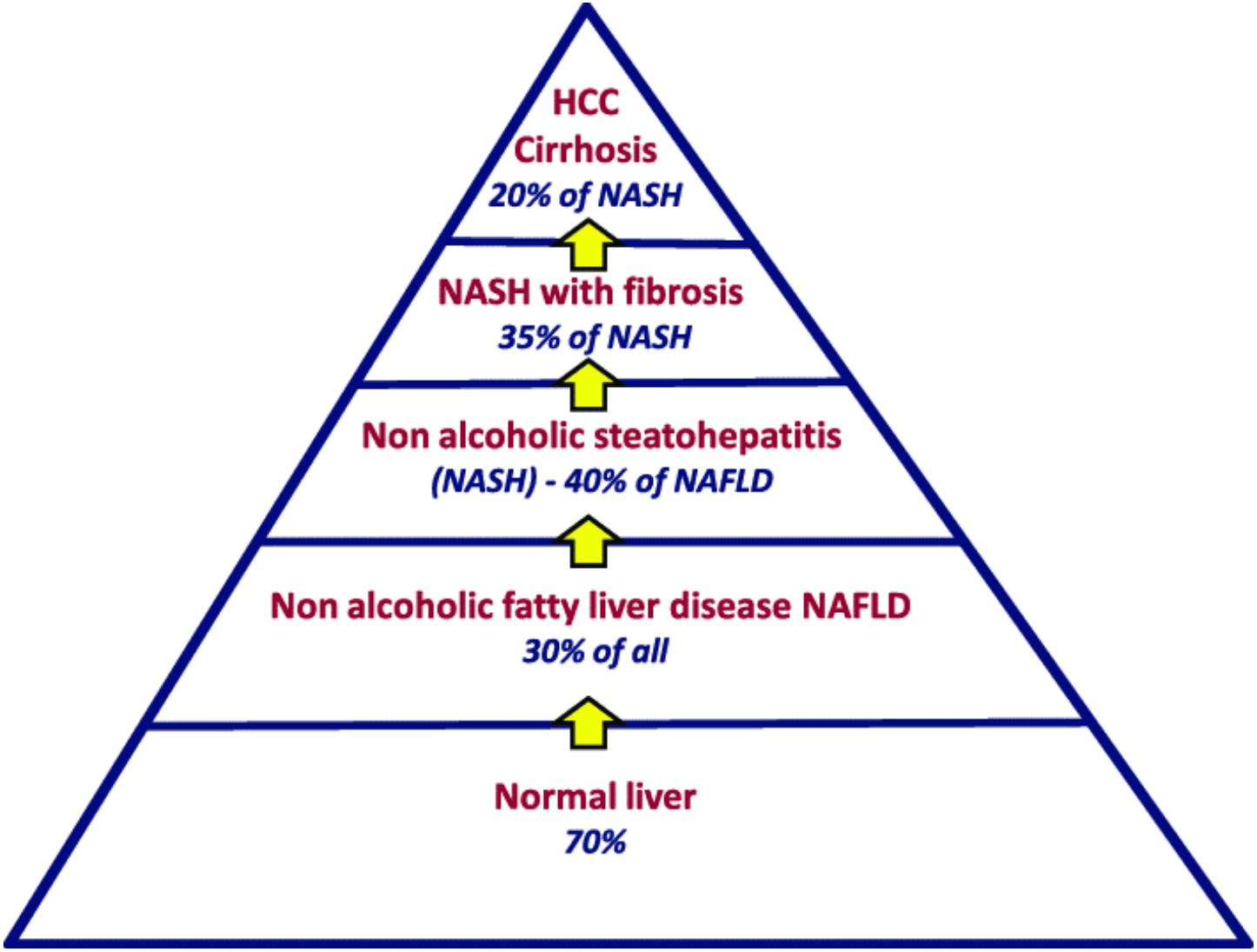
Fat plus inflammation and scarring

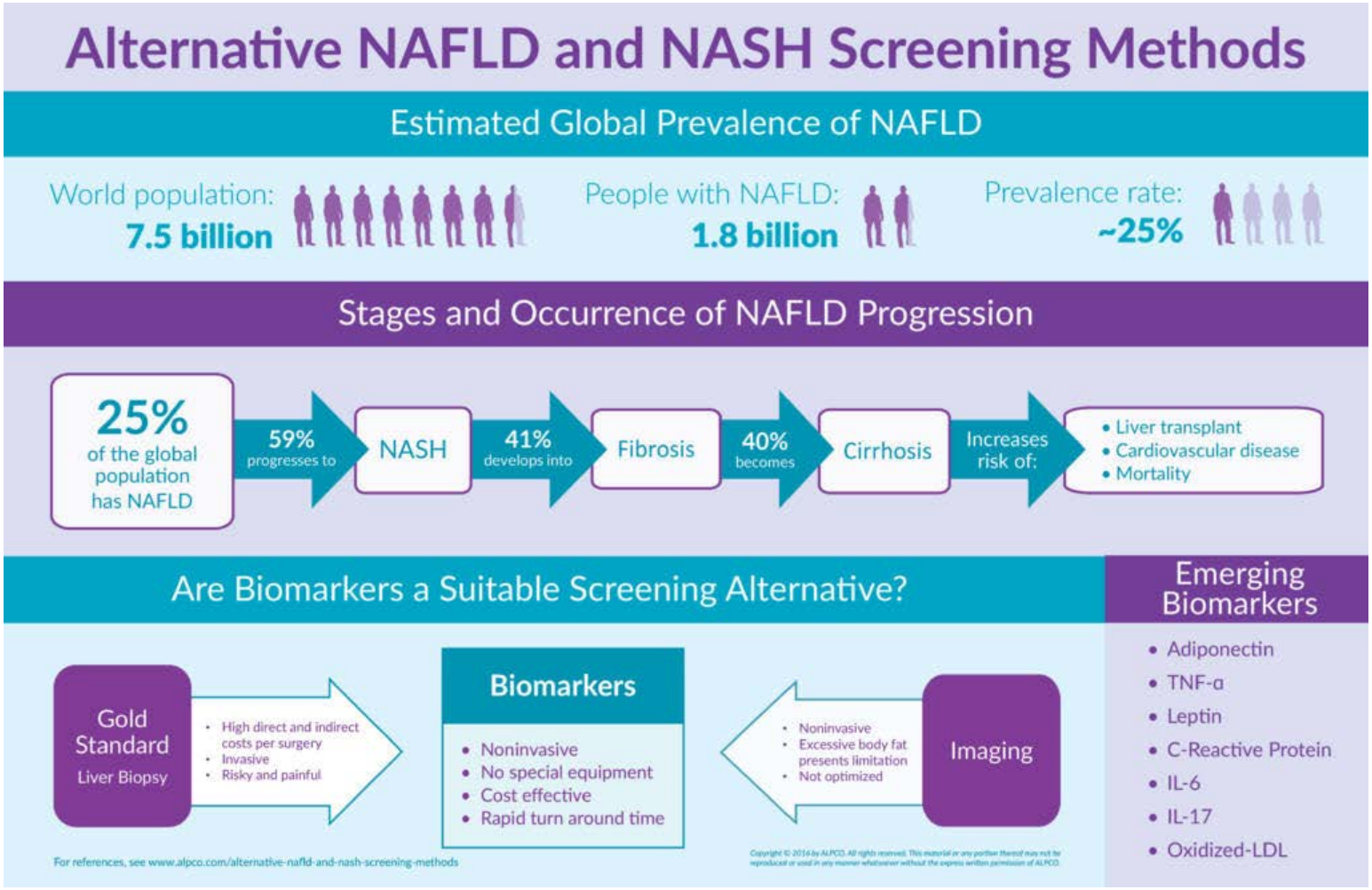
## Cirrhosis



Scar tissue replaces liver cells


Healthy Liver
NAFLD
NASH
Cirrhosis
Reversible
Reversible
Irreversible
Hepatocyte
Nucleus
Small droplets of fat
Bloated hepatocyte
Large droplets of fat
Displaced nucleus
Collagen fibers
Inflamed dying hepatocyte
Scarring
Remnant of dead cells


HCC
Cirrhosis
20% of NASH
NASH with fibrosis
35% of NASH
Non alcoholic steatohepatitis
(NASH) - 40% of NAFLD
Non alcoholic fatty liver disease NAFLD
30% of all
Normal liver
70%


Alternative NAFLD and NASH Screening Methods
Estimated Global Prevalence of NAFLD
World population:
7.5 billion
People with NAFLD:
1.8 billion
Prevalence rate:
~25%
Stages and Occurrence of NAFLD Progression
25%
of the global population has NAFLD
59%
progresses to
NASH
41%
develops into
Fibrosis
40%
becomes
Cirrhosis
Increases risk of:
• Liver transplant
• Cardiovascular disease
• Mortality
Are Biomarkers a Suitable Screening Alternative?
Gold Standard
Liver Biopsy
• High direct and indirect costs per surgery
• Invasive
• Risky and painful
Biomarkers
• Noninvasive
• No special equipment
• Cost effective
• Rapid turn around time
Imaging
• Noninvasive
• Excessive body fat presents limitation
• Not optimized
For references, see www.alpco.com/alternative-nafld-and-nash-screening-methods
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Emerging Biomarkers
• Adiponectin
• TNF-α
• Leptin
• C-Reactive Protein
• IL-6
• IL-17
• Oxidized-LDL

# Fatty livers

## Fatty livers fall into two main categories

- A) More **synthesis** of Triglycerides
  - High carbohydrate diet
  - High fat feeding
  - Starvation
  - Diabetes mellitus
- High carbohydrate diet stimulates de novo fatty acid synthesis by providing excess of Acetyl CoA
- High fat feeding provides more flux of fatty acids from the diet that can be esterifies to provide excess triglycerides

# Fatty livers (cont.)

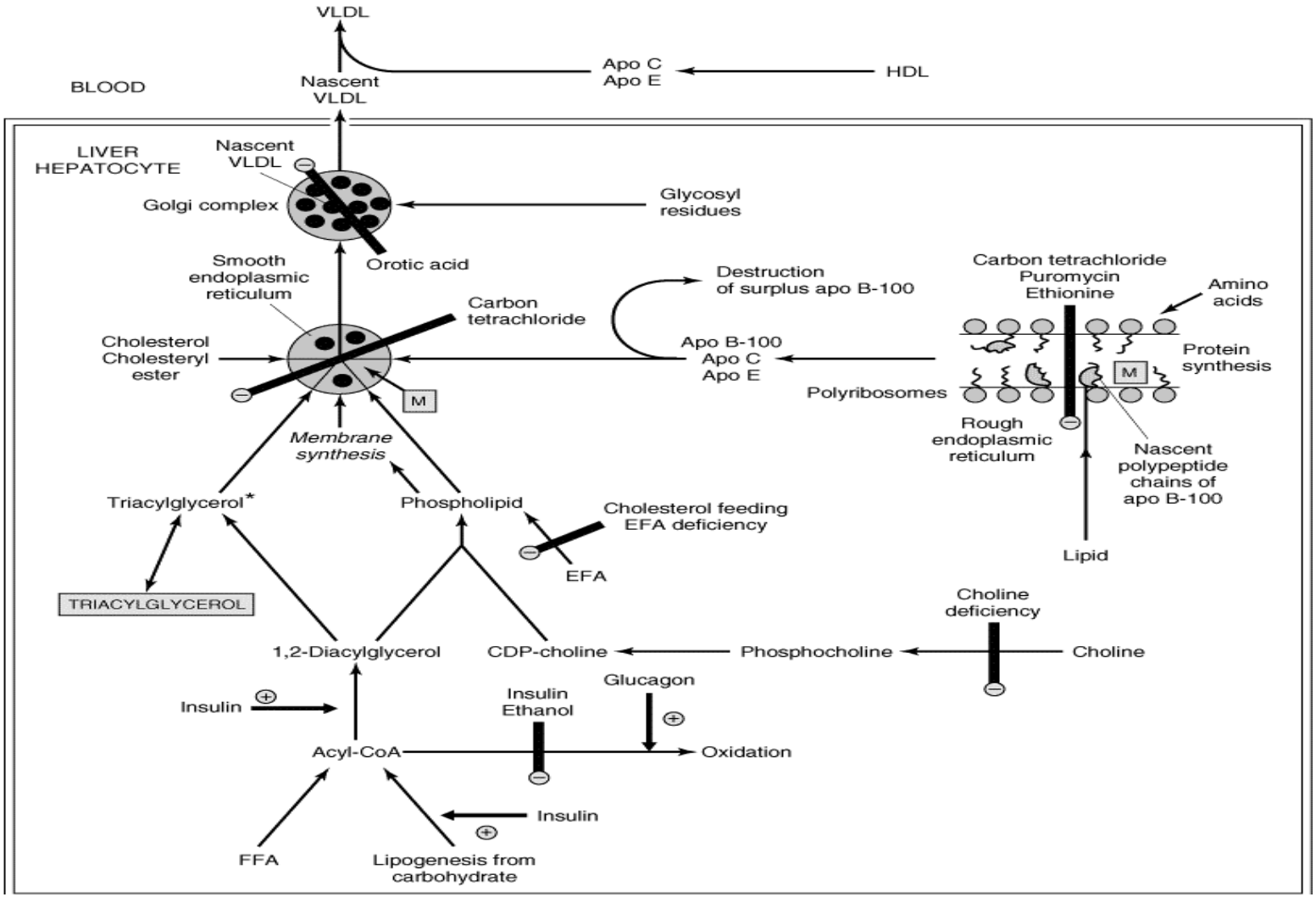
- B) Defective VLDL synthesis
- The second type of fatty liver is usually due to a **metabolic block in the production of plasma lipoproteins,** thus allowing triacylglycerol to accumulate.
- The lesion may be due to
- **(1)A block in apolipoproteins synthesis**
  - a) Protein energy Malnutrition
  - b) Impaired absorption
  - c) Presence of inhibitors of endogenous protein synthesis e.g. Carbon tetra chloride, Puromycin, Ethionine , Heavy metals etc.
  - d) Hypobetalipoproteinemia- Defective apo B gene can cause impaired synthesis of apo B protein.

# Fatty livers

- (2) A failure in provision of phospholipids that are found in lipoproteins
  - a) A deficiency of **choline,** a **lipotropic factor** can cause impaired formation of phosphatidyl choline (Lecithin), a glycerophospholipid.
  - b) Methionine deficiency can also cause impaired choline synthesis
  - c) Inositol deficiency
  - d) Deficiency of essential fatty acids can also cause impaired PL synthesis

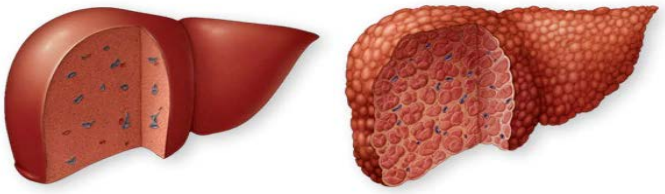
# Fatty livers

- (3) Impaired Glycosylation
- Orotic acid also causes fatty liver; it interferes with glycosylation of the lipoprotein, thus inhibiting release, and may also impair the recruitment of triacylglycerol to the particles.
- In conditions of Orotic aciduria (disorder of pyrimidine nucleotide biosynthesis), fatty liver can be observed.
- **4**) Impaired secretion of VLDL
- oxidative stress is a common cause for membrane disruption of lipoproteins.

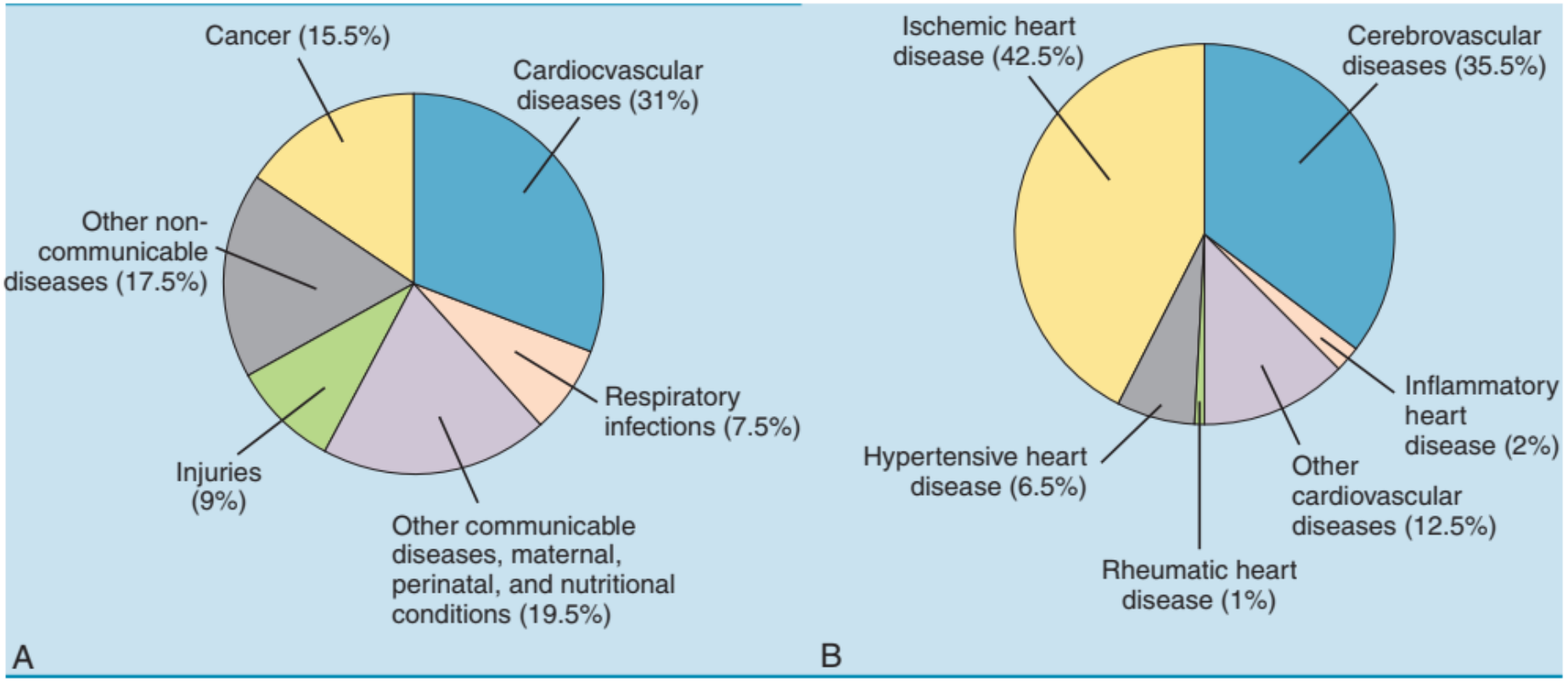

VLDL
BLOOD
Nascent VLDL
Apo C
Apo E
HDL
LIVER HEPATOCYTE
Nascent VLDL
Golgi complex
Glycosyl residues
Orotic acid
Smooth endoplasmic reticulum
Carbon tetrachloride
Destruction of surplus apo B-100
Carbon tetrachloride
Puromycin
Ethionine
Amino acids
Cholesterol
Cholesteryl ester
Apo B-100
Apo C
Apo E
Protein synthesis
Polyribosomes
M
Membrane synthesis
Rough endoplasmic reticulum
Nascent polypeptide chains of apo B-100
Triacylglycerol*
Phospholipid
Cholesterol feeding
EFA deficiency
EFA
Lipid
TRIACYLGLYCEROL
Choline deficiency
1,2-Diacylglycerol
CDP-choline
Phosphocholine
Choline
Glucagon
Insulin
Insulin
Ethanol
Acyl-CoA
Oxidation
Insulin
FFA
Lipogenesis from carbohydrate

# 2) Alcoholic fatty liver

- **Alcoholism** leads to fat accumulation in the liver, hyperlipidemia, and ultimately cirrhosis.
- The fatty liver is caused by a combination of impaired fatty acid oxidation and increased lipogenesis, which is thought to be due to changes in the [NADH]/ [NAD+] redox potential in the liver,
- and also to interference with the action of transcription factors regulating the expression of the enzymes involved in the pathways



# Causes of death worldwide in 2010



# The main and emerging cardiovascular risk factors

| | |
|---|---|
| Male sex | Cardiovascular risk between sexes equalizes in postmenopausal women. |
| Age | In elderly people, age and gender alone may determine the high risk. |
| Smoking | |
| Hypertension | |
| High plasma total cholesterol | |
| High LDL-cholesterol | |
| Low plasma HDL-cholesterol | |
| Diabetes mellitus | CVD is the main cause of death in diabetes. |
| Impaired renal function | |

| | |
|---|---|
| Family history of premature ASCVD | Positive family history of premature CVD increases the calculated risk by a factor of 1.7–2.0. |
| High plasma apoB | |
| Low plasma apoA | Newer studies show that prediction of risk based on apolipoproteins is better than that based on cholesterol concentration. |
| High lp(a) | Refines risk assessment |
| High hsCRP/fibrinogen | Refine risk assessment |
| Low adiponectin | Important in obesity and diabetes |
| Central obesity | |
| Sedentary lifestyle | |
| Increased carotid intima-media thickness | |
| Social deprivation | |
| Autoimmune inflammatory conditions (rheumatoid arthritis, SLE, psoriasis) | |

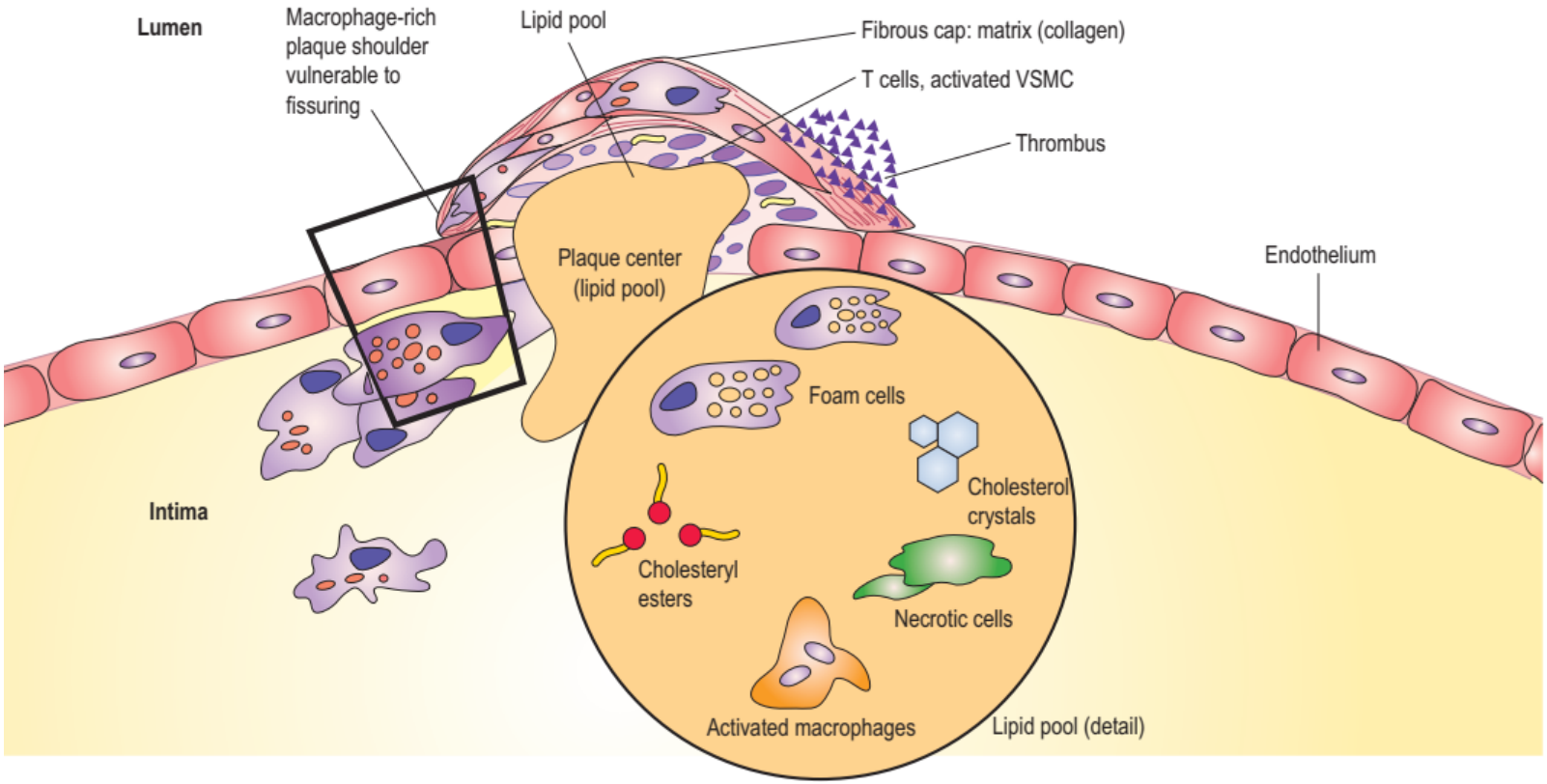
# ATHEROSCLEROSIS

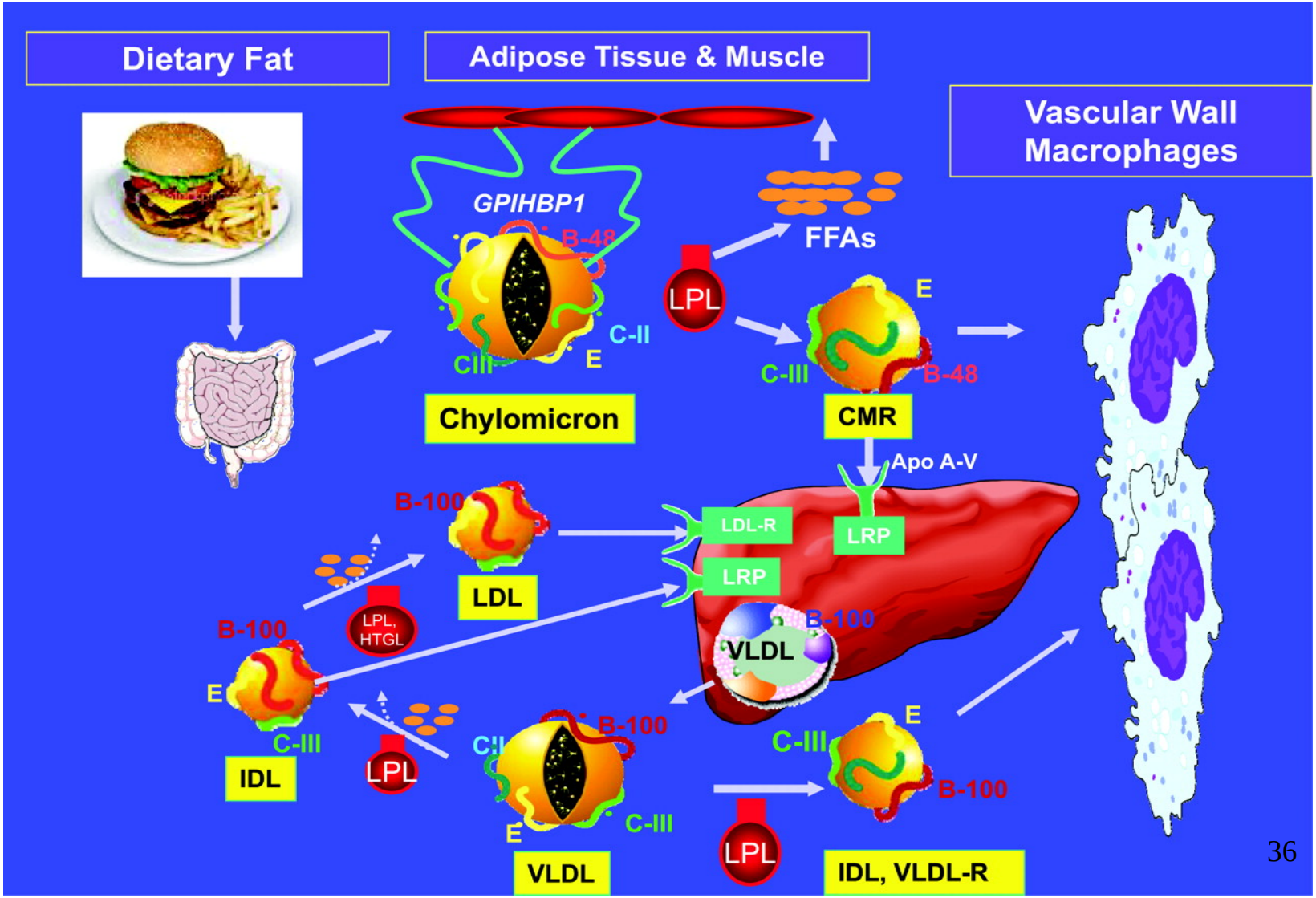
- ASCVD is presently the most frequent cause of death in the world; ischemic heart disease and cerebrovascular disease are together responsible for 23.6% of all deaths worldwide (WHO 2011). **Atherogenesis** is a process that leads to the narrowing, or a sudden complete occlusion, of the arterial lumen. The result is ASCVD. An occlusion

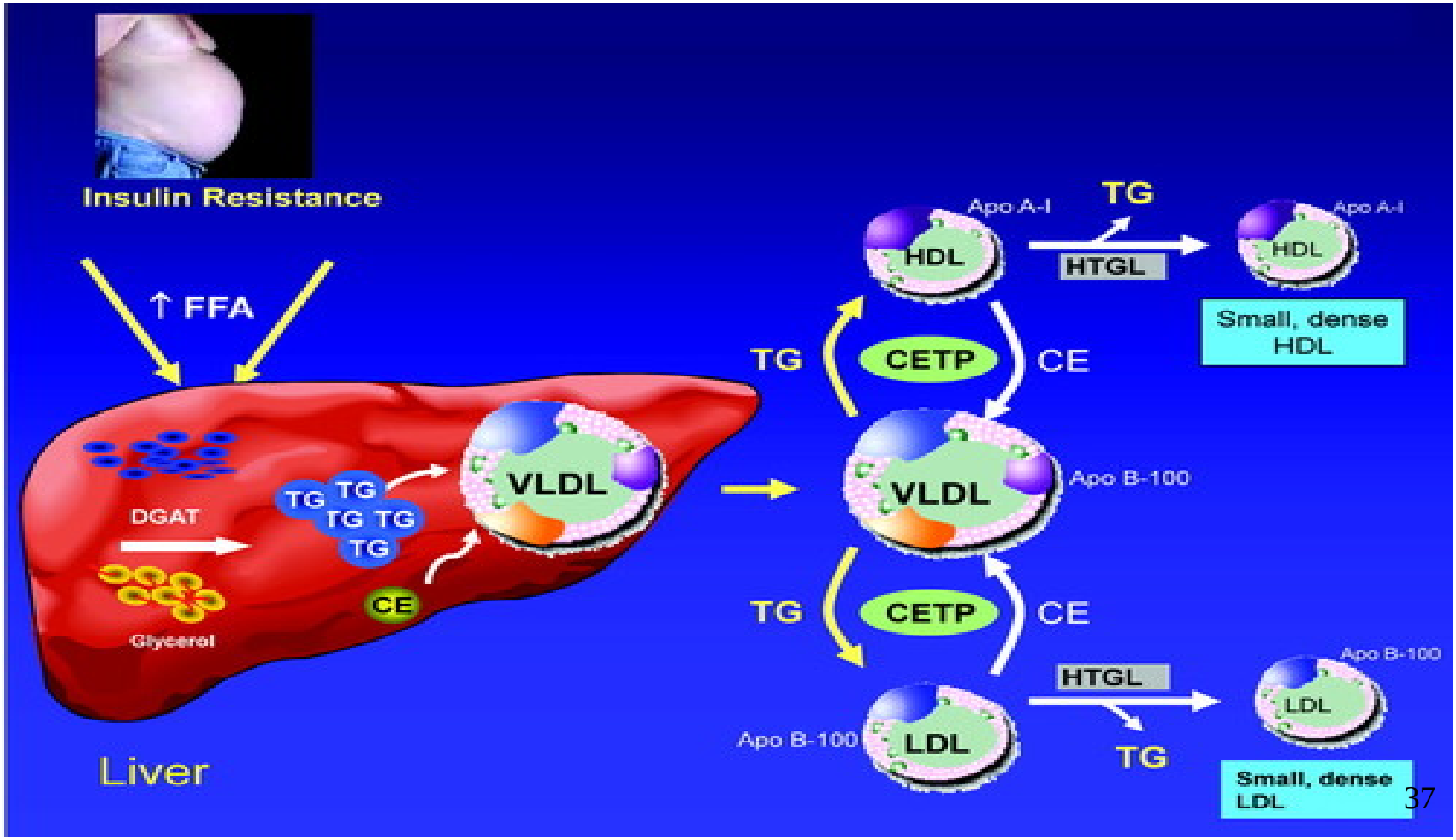
  may cause **myocardial**

- **infarction** (if the blockage is in a coronary artery), **stroke** (blockage in an artery supplying the brain), or **peripheral vascular disease** (blockage in leg arteries; this leads to characteristic pain that occurs during walking, with fast relief

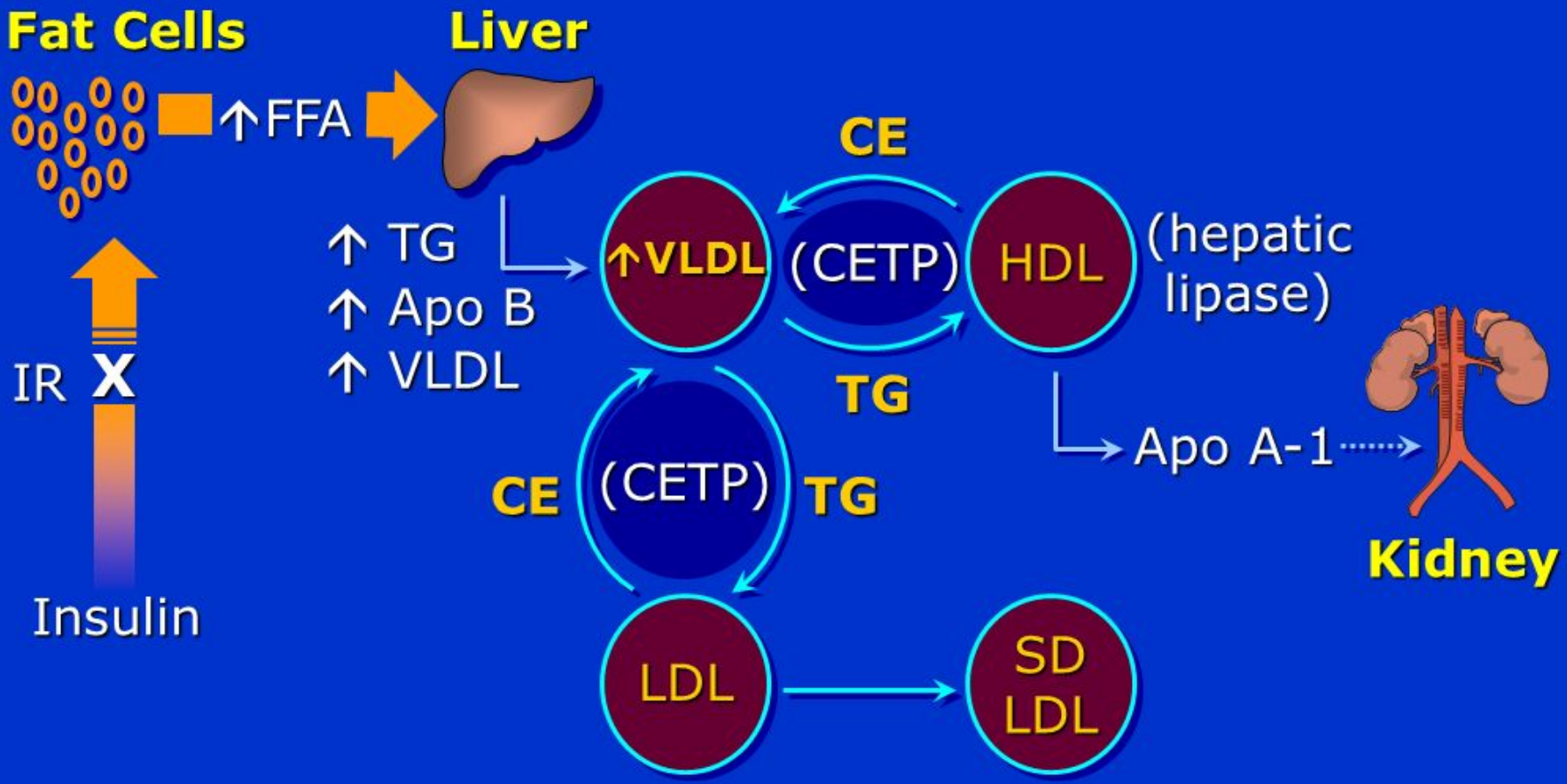
  on stopping, known as intermittent claudication)


Lumen
Macrophage-rich plaque shoulder vulnerable to fissuring
Lipid pool
Fibrous cap: matrix (collagen)
T cells, activated VSMC
Thrombus
Plaque center (lipid pool)
Endothelium
Intima
Foam cells
Cholesterol crystals
Cholesteryl esters
Necrotic cells
Activated macrophages
Lipid pool (detail)


Dietary Fat
Adipose Tissue & Muscle
Vascular Wall Macrophages
GPIHBP1
B-48
C-II
CIII
E
Chylomicron
LPL
FFAs
E
C-III
B-48
CMR
Apo A-V
LRP
LDL-R
LRP
B-100
LDL
B-100
VLDL
LPL, HTGL
B-100
E
C-III
IDL
LPL
CII
B-100
E
C-III
VLDL
LPL
E
C-III
B-100
IDL, VLDL-R


Insulin Resistance
↑ FFA
DGAT
TG TG
TG TG
TG
CE
Glycerol
VLDL
Liver
TG
CETP
CE
HDL
Apo A-I
HTGL
HDL
Apo A-I
Small, dense HDL
VLDL
Apo B-100
TG
CETP
CE
HTGL
LDL
Apo B-100
TG
LDL
Apo B-100
Small, dense LDL

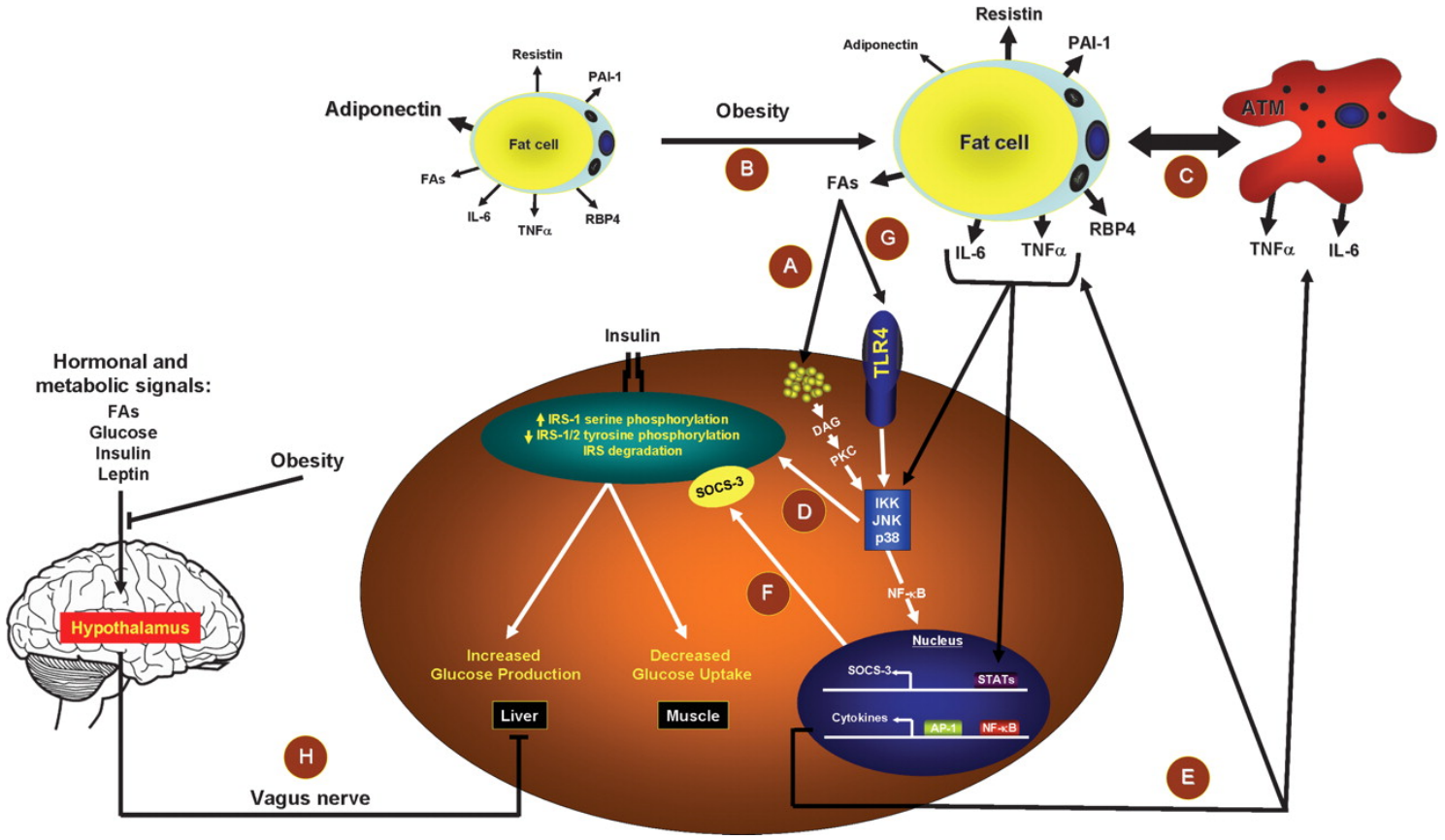
# Mechanisms Relating Insulin Resistance and Dyslipidemia




Thanks for your attention

# Extra Cellular Mechanism

**Endocrine, inflammatory, and neuronal pathways link obesity to insulin resistance**

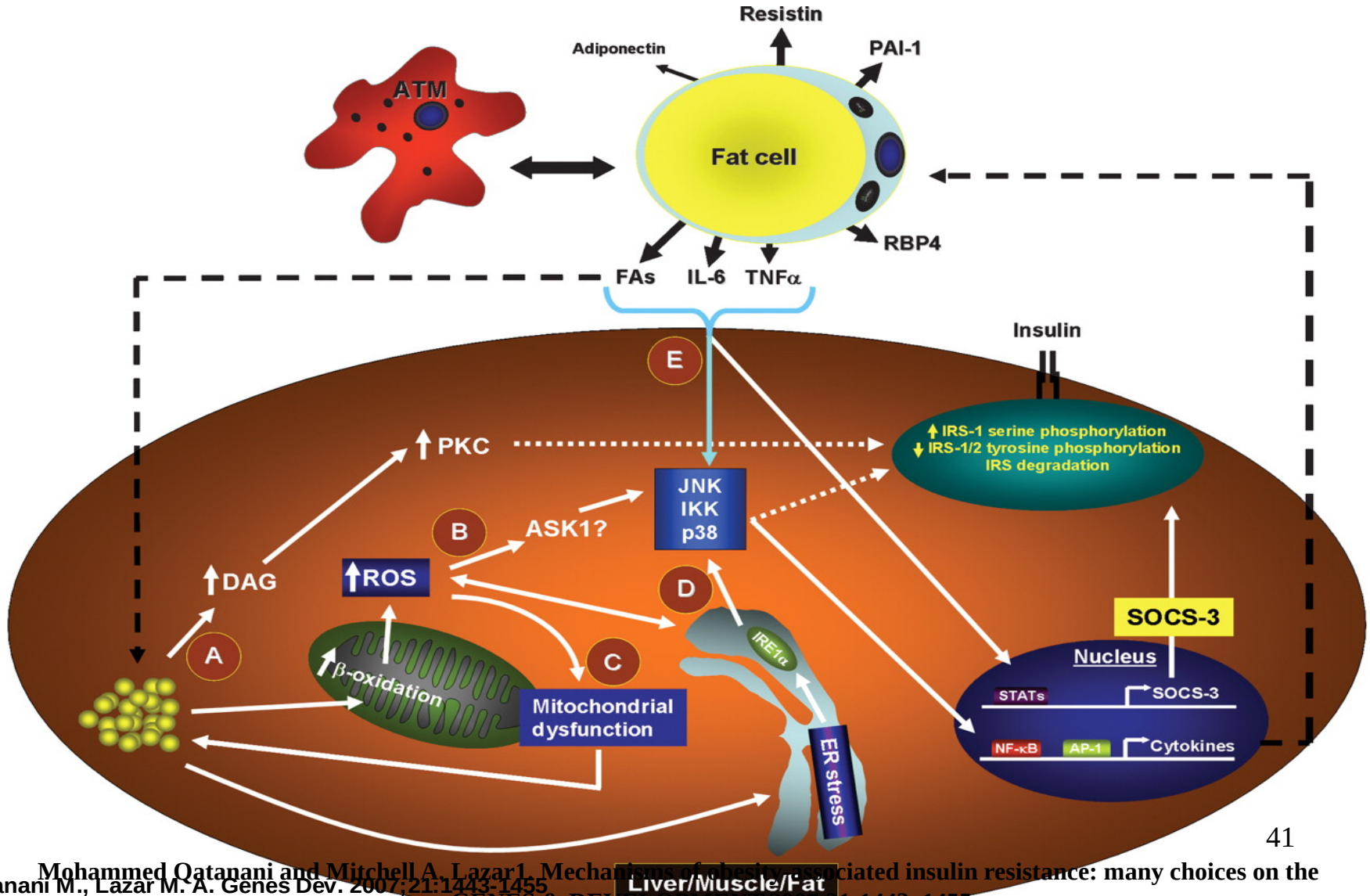



Qatanani M., Lazar M. A. Genes Dev. 2007;21:1443-1455

Mohammed Qatanani and Mitchell A. Lazar1. Mechanisms of obesity-associated insulin resistance: many choices on the menu,GENES & DEVELOPMENT,2007 21:1443–1455

# Cell-intrinsic Mechanisms

**Obesity-associated intrinsic mediators of insulin resistance**



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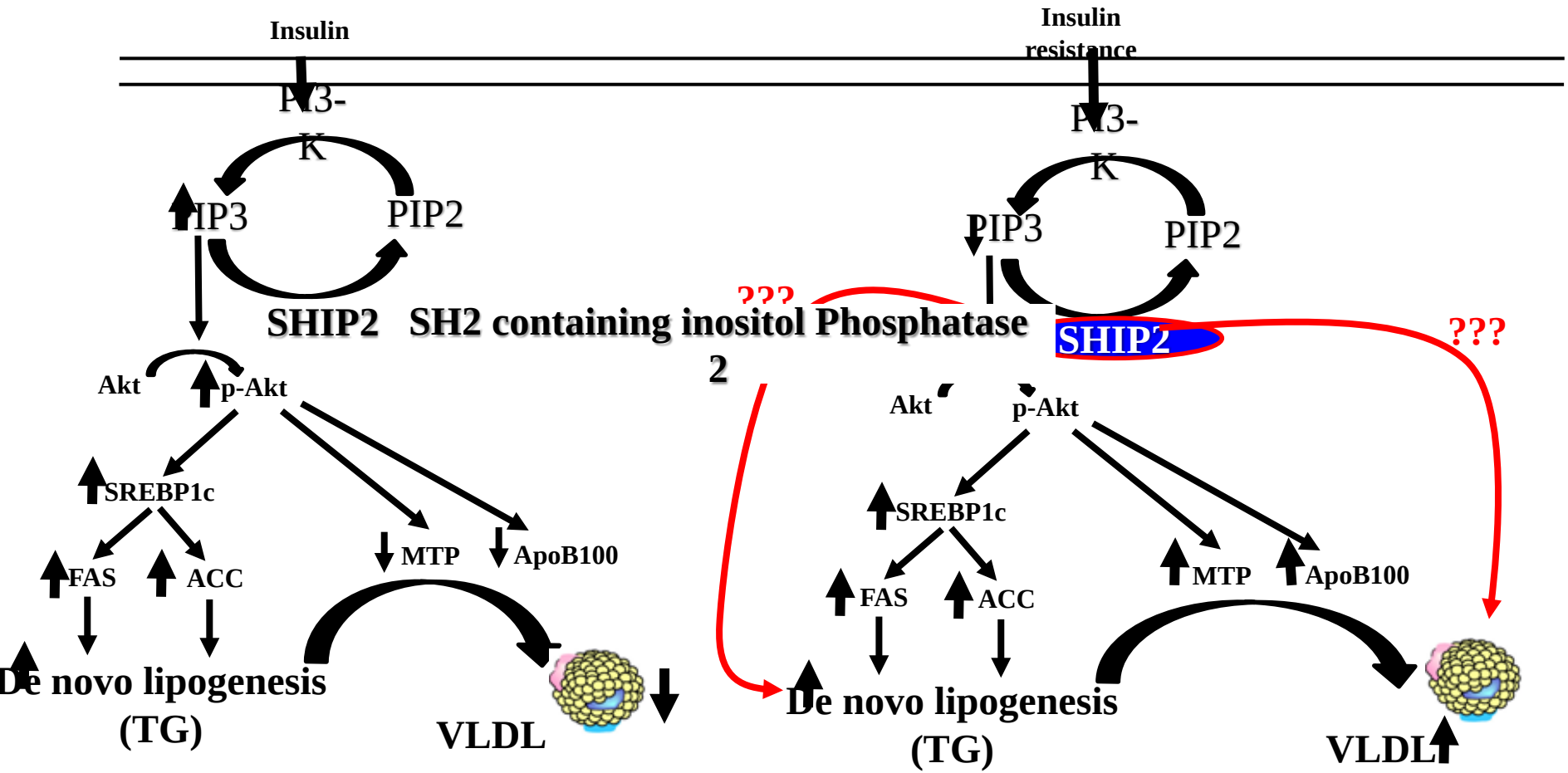
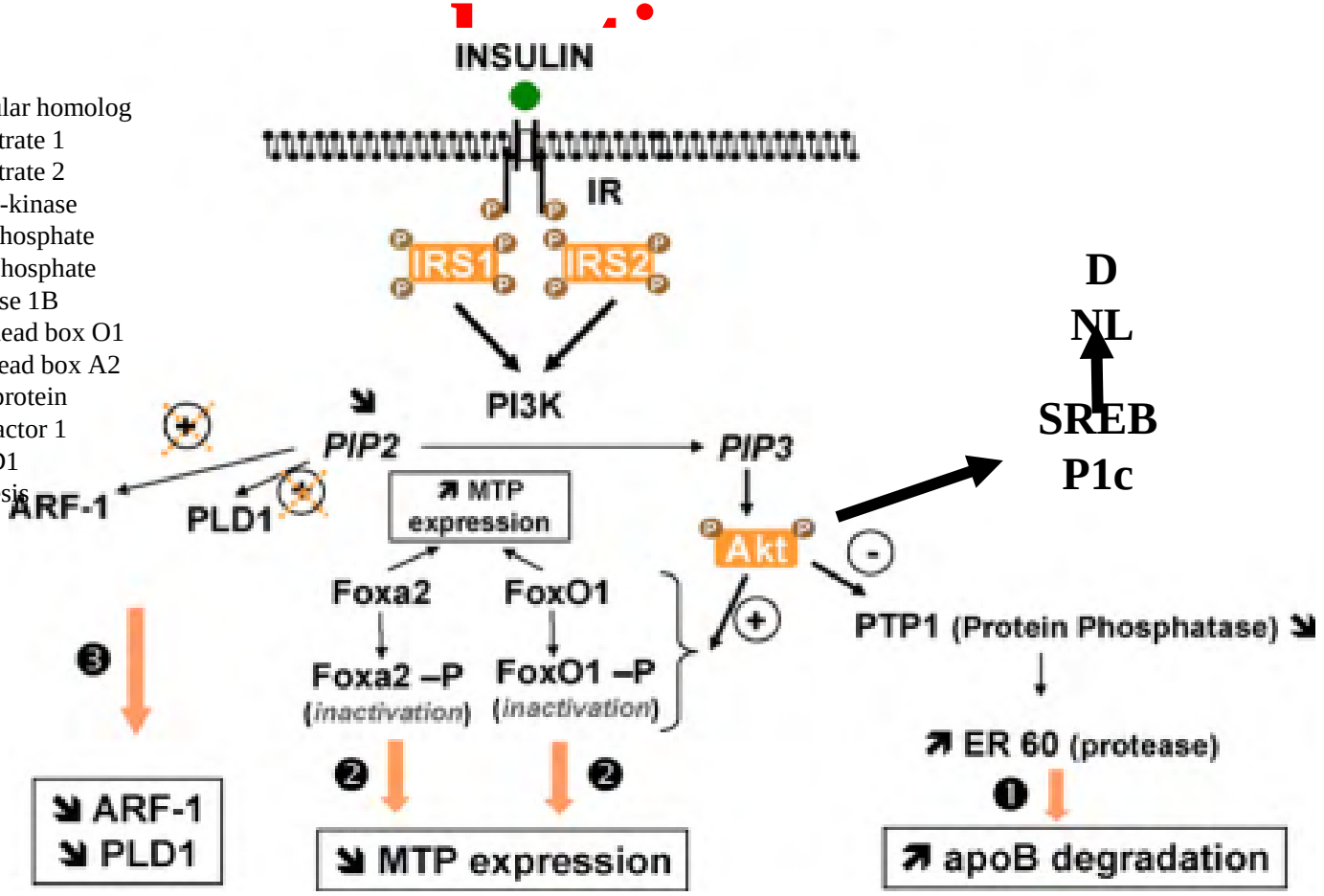
# Role of SHIP2 in insulin signaling and lipogenesis



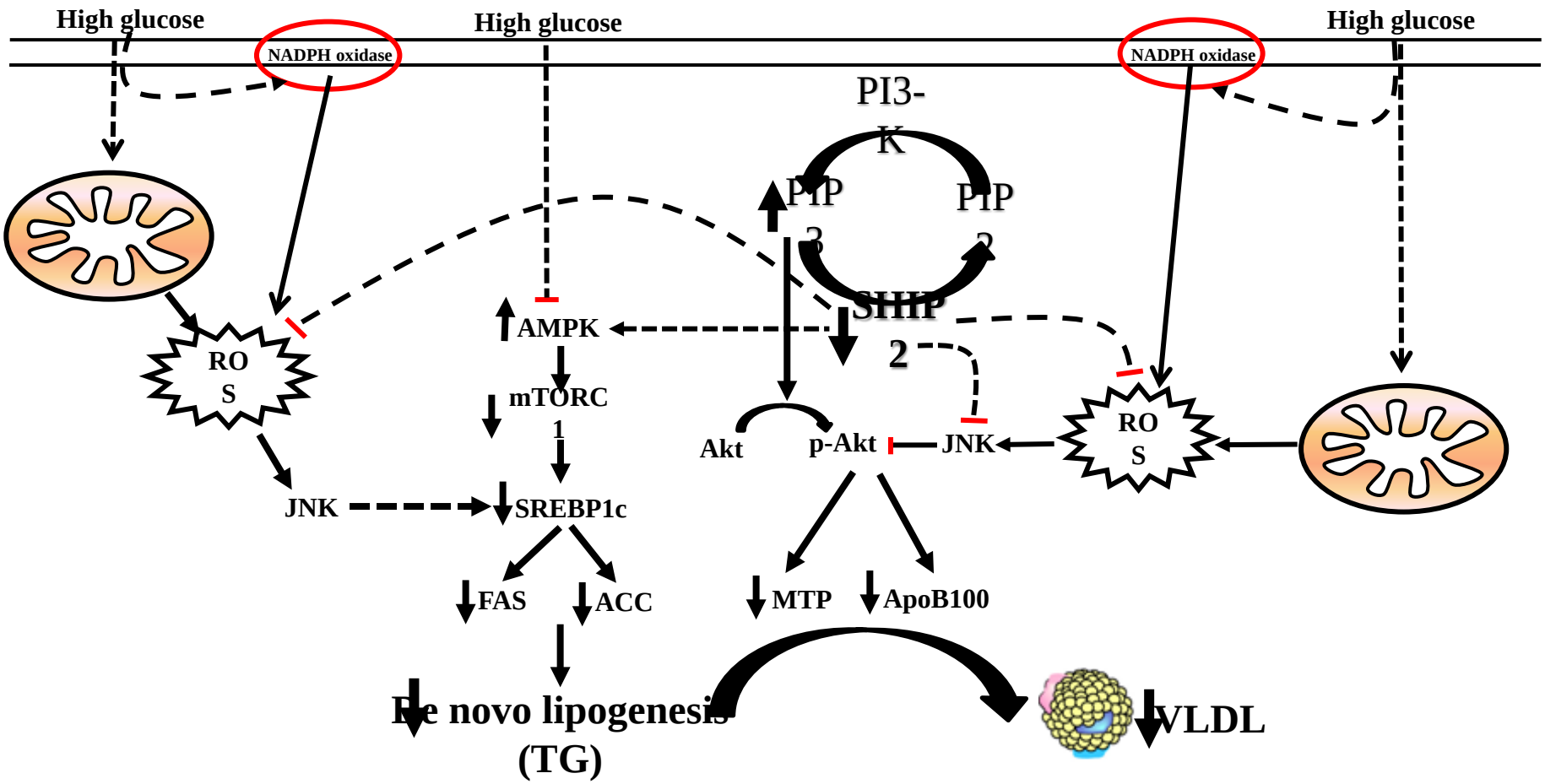
# Direct role of insulin in VLDL

AKT: AKT8 virus oncogene cellular homolog
IRS1: insulin receptor Substrate 1
IRS2: insulin receptor Substrate 2
PI3K: phosphatidylinositol 3-kinase
PIP2: phosphatidylinositol biphosphate
PIP3: phosphatidylinositol triphosphate
PTP 1B: protein phosphatase 1B
FoxO1: transcription factor forkhead box O1
Foxa2: transcription factor forkhead box A2
MTP: microsomal transfer protein
ARF-1: ADP ribosylation factor 1
PLD1: phospholipase D1
DNL: De-novo lipogenesis




**Bruno Vergès. *Atherosclerosis* 211 (2010) 353–360**

# Conclusion


High glucose
NADPH oxidase
High glucose
NADPH oxidase
High glucose
PI3-K
PIP 3
PIP 2
SHIP 2
AMPK
mTORC 1
RO S
RO S
JNK
SREBP1c
Akt
p-Akt
JNK
FAS
ACC
MTP
ApoB100
De novo lipogenesis (TG)
VLDL

# References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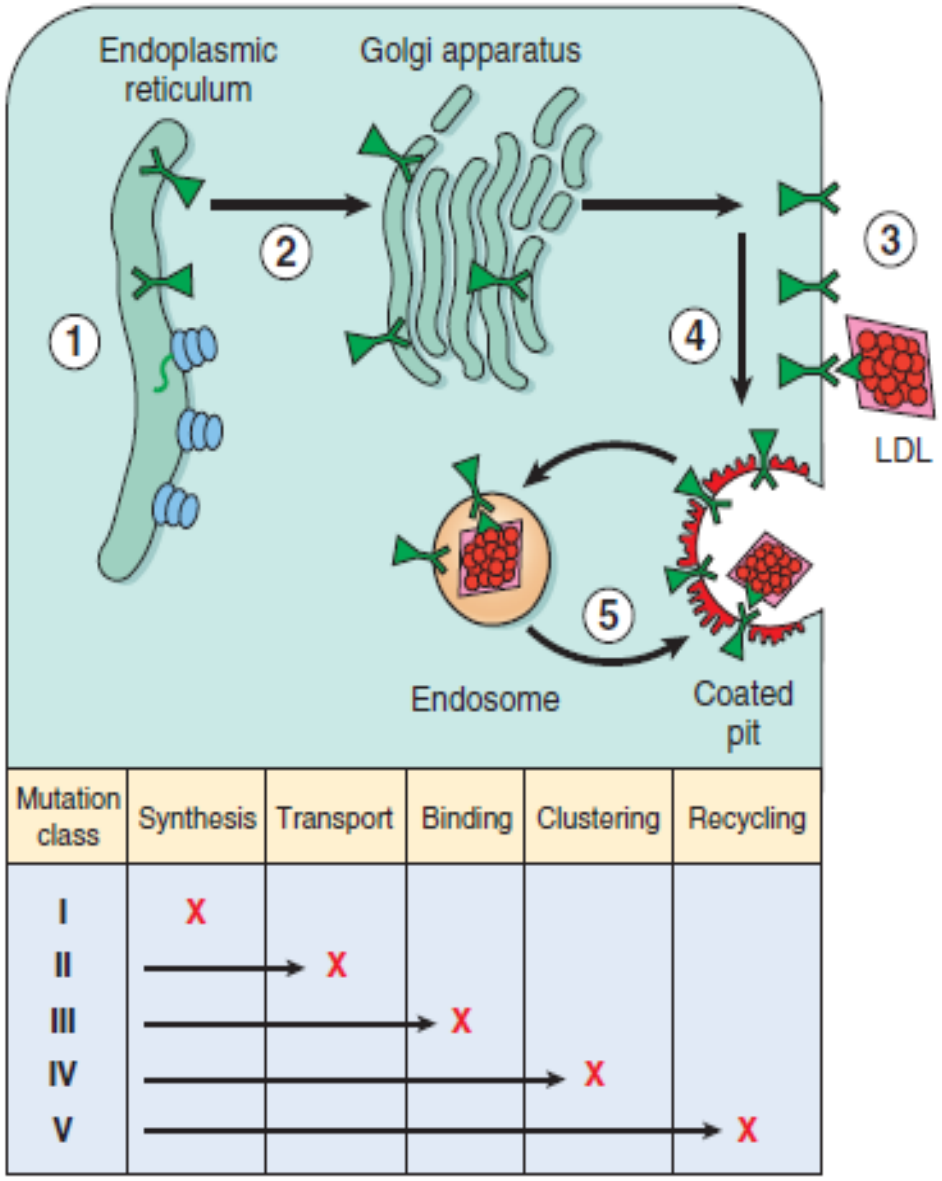
# Familial Hypercholesterolemia




| Mutation class | Synthesis | Transport | Binding | Clustering | Recycling |
|---|---|---|---|---|---|
| I | X | | | | |
| II | → | X | | | |
| III | → | → | X | | |
| IV | → | → | → | X | |
| V | → | → | → | → | X |

**Class I:** LDLR is not synthesized at all.
**Class II:** LDLR is not properly transported from the endoplasmic reticulum to the Golgi apparatus for expression on the cell surface.

**Class III:** LDLR does not properly bind LDL on the cell surface because of a defect in either apoB-100 (R3500Q) or in the LDLR.

**Class IV**: LDLR bound to LDL does not properly cluster in clathrincoated pits for receptor-mediated endocytosis.

**Class V**: LDLR is not recycled back to the cell surface.