UNIVERSITA' DEGLI STUDI DI PERUGIA
DIPARTIMENTO DI MEDICINA E CHIRURGIA

SANU AA 2023/24

Approach to patient with liver disease
Alcoholic liver disease
NAFLD & NASH

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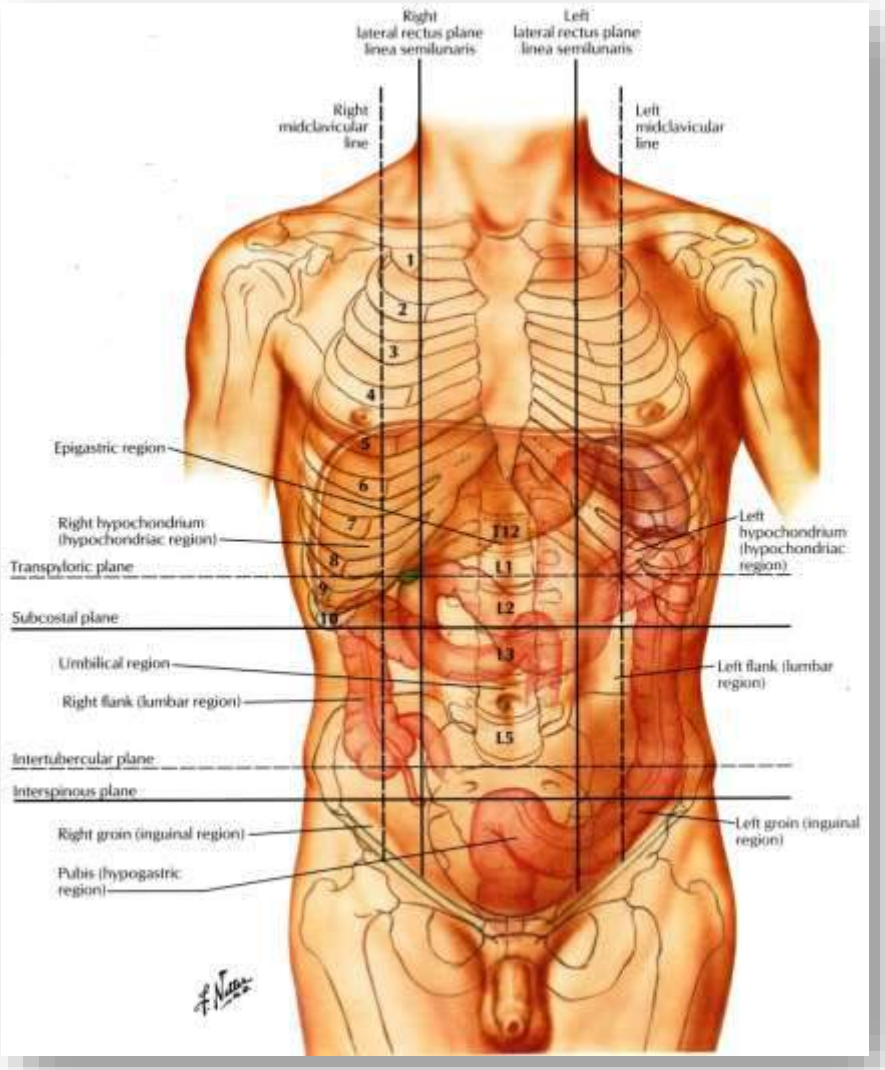
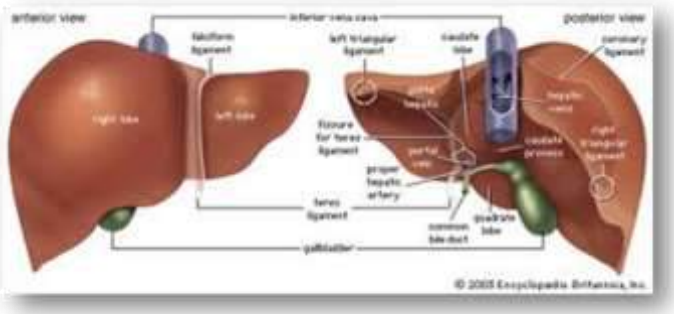
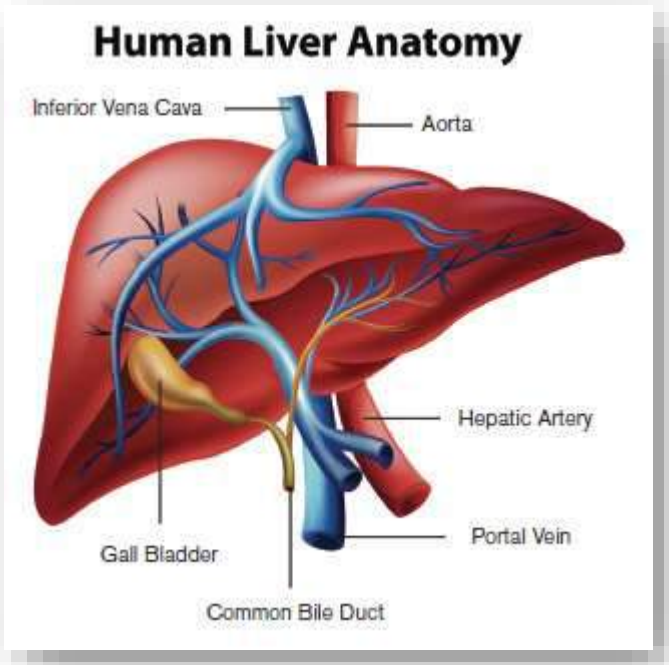
Liver anatomy

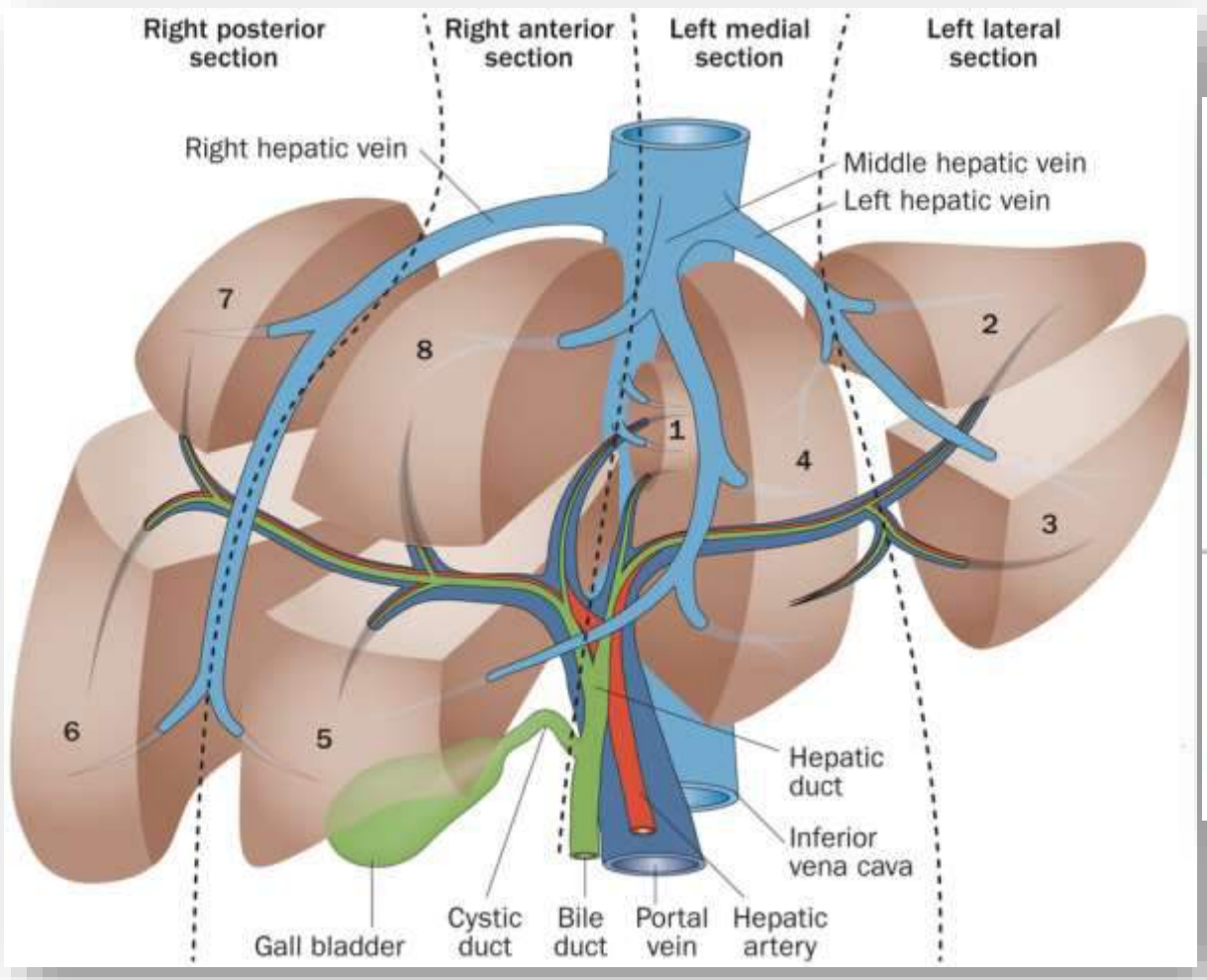
Liver anatomy

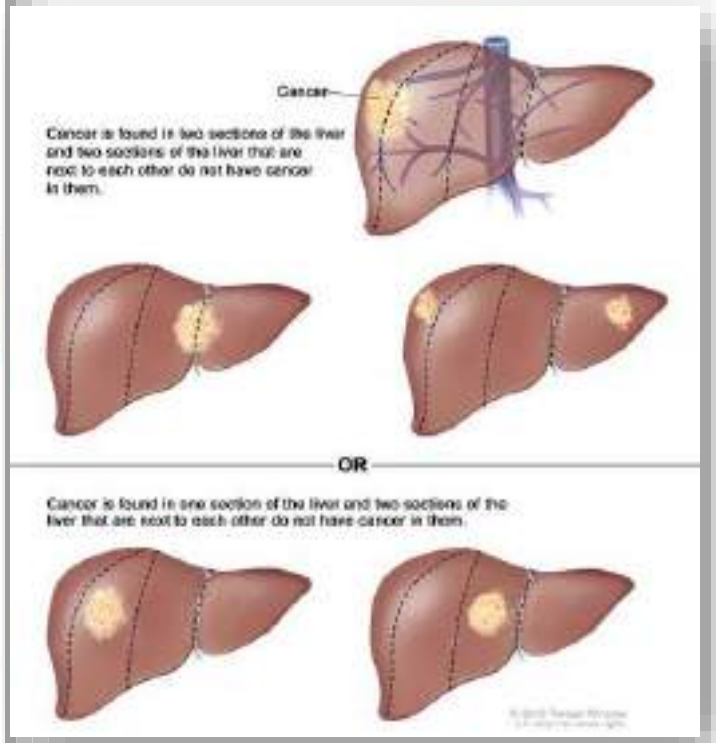




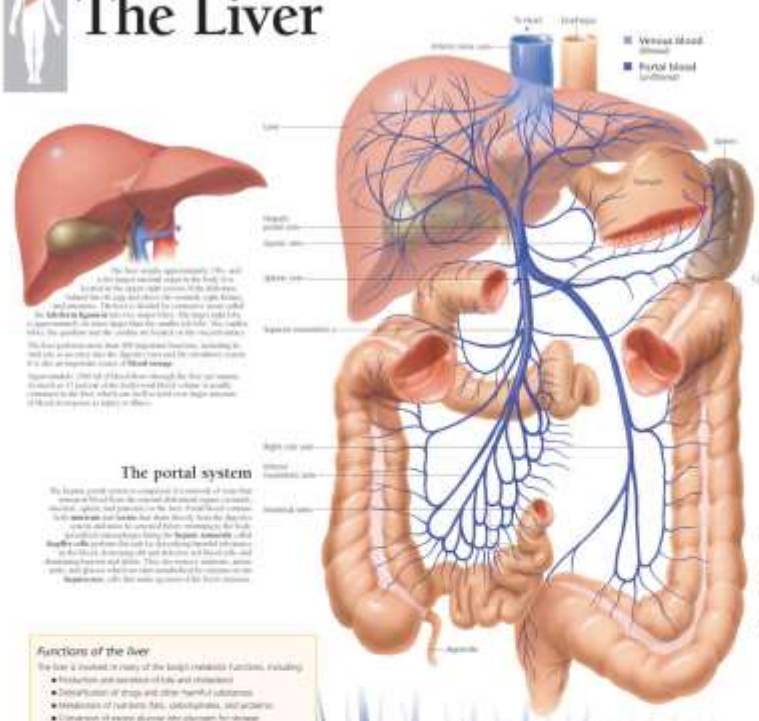


Hepatic lobules by Coinaud





The Liver



Bile production

Bile ducts

Visceral surface

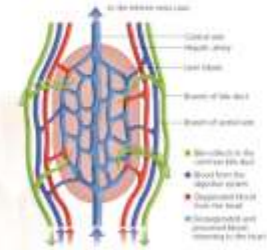
The portal system

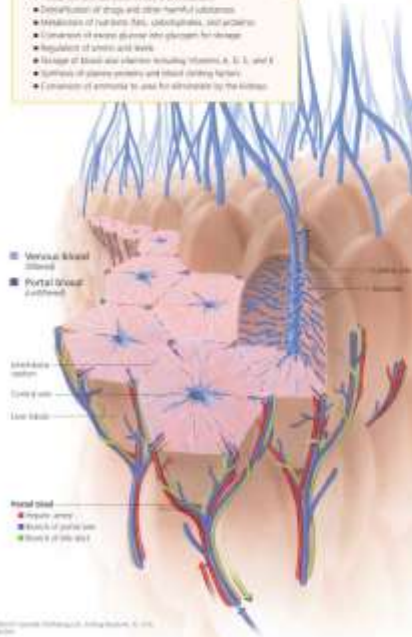
Functions of the liver

The liver is involved in many of the body's metabolic functions, including:

- Production and secretion of bile and cholesterol
- Detoxification of drugs and other harmful substances
- Metabolism of fuel from fats, carbohydrates, and proteins
- Conversion of excess glucose into glycogen for storage
- Regulation of amino acid levels
- Storage of blood and vitamins including vitamins A, D, E, and K
- Synthesis of plasma proteins and blood clotting factors
- Conversion of ammonia to urea for elimination by the kidneys

Liver lobule function

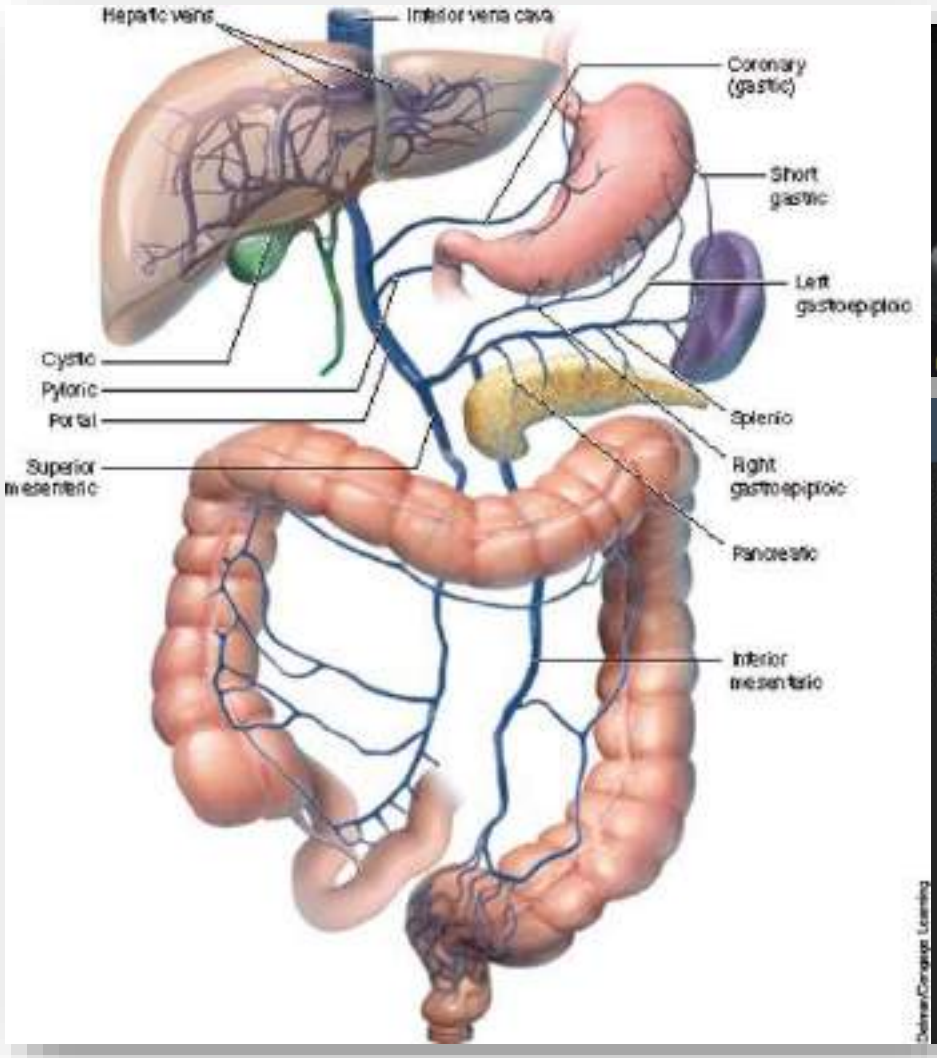


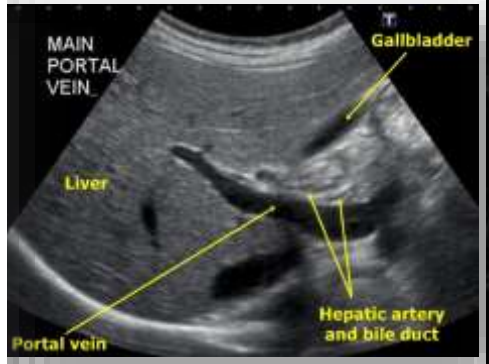


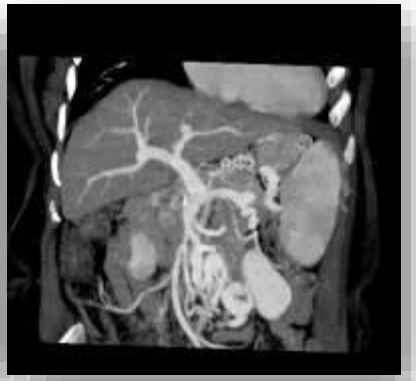
Enlarged view of the liver lobule

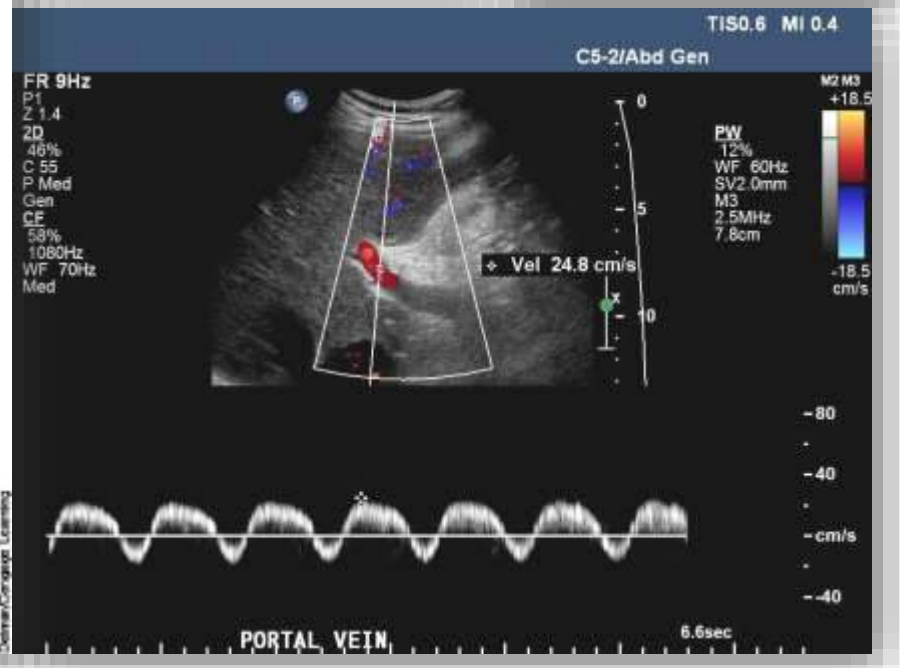
Structure of the liver

Portal vein anatomy and pathology

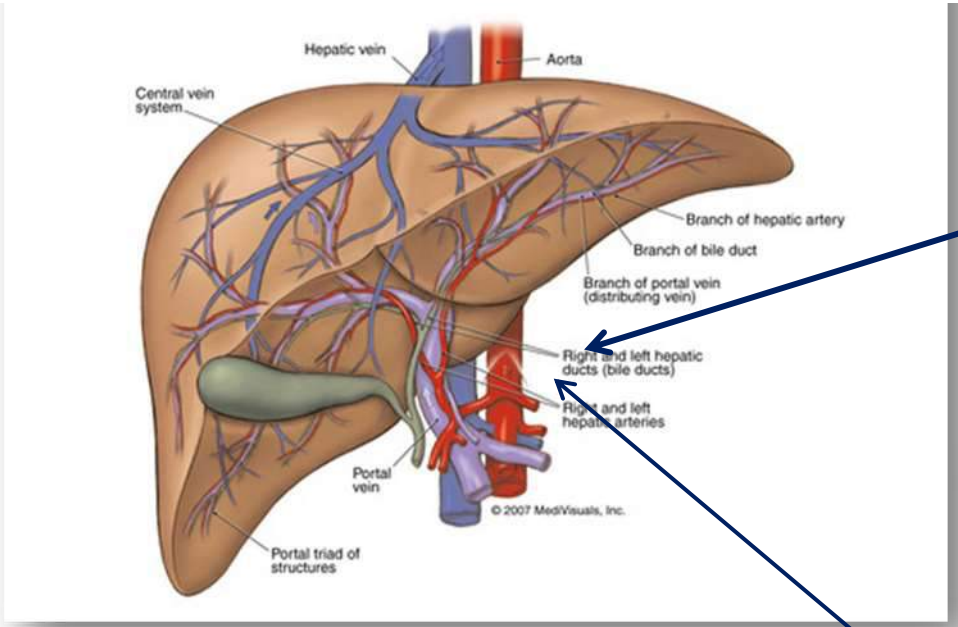


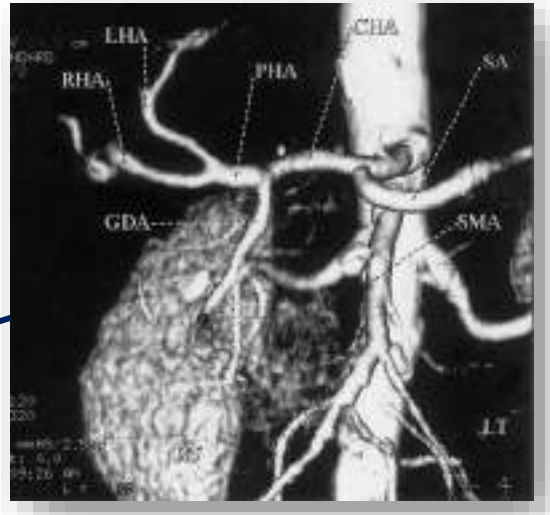


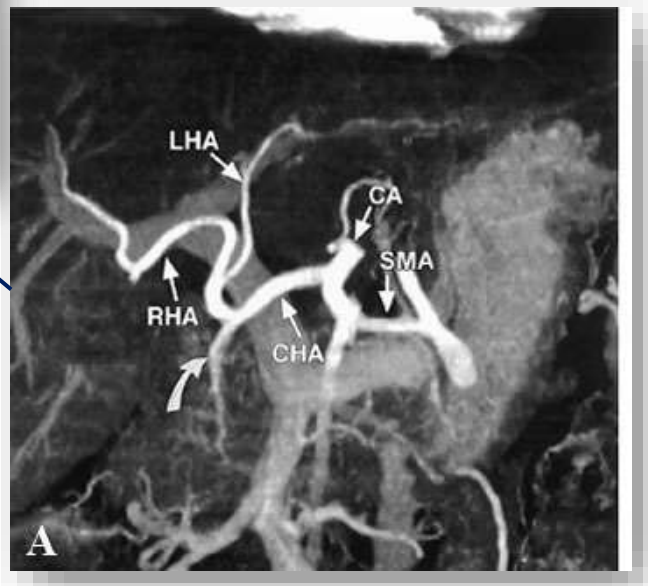




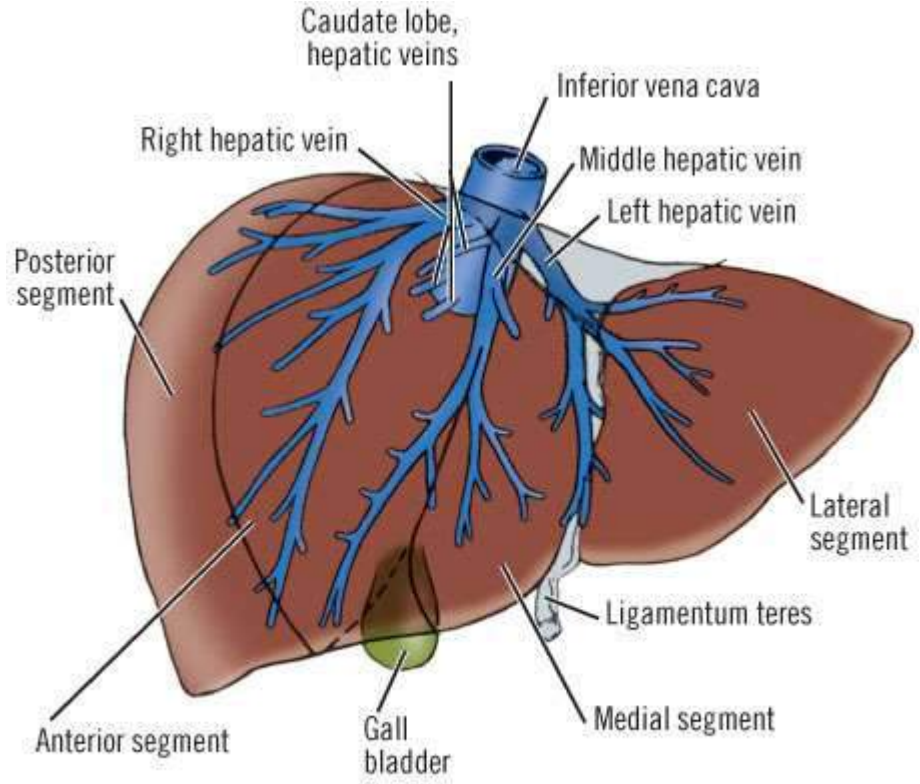
Hepatic artery

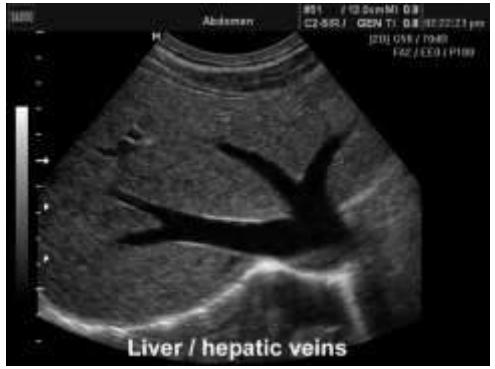


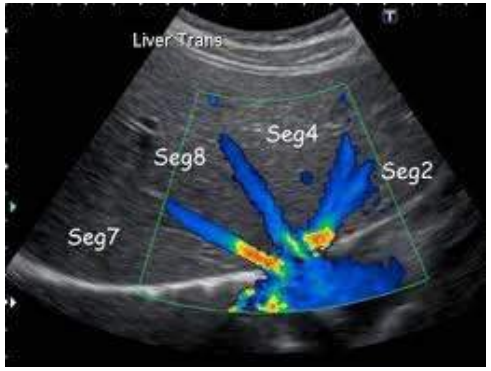


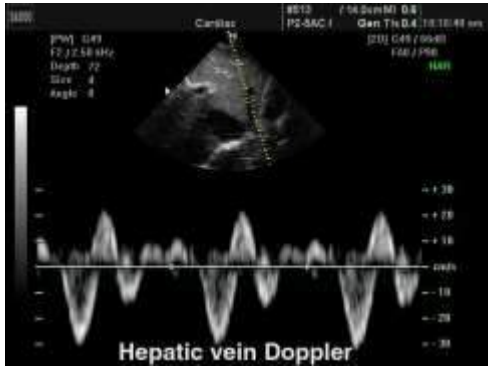


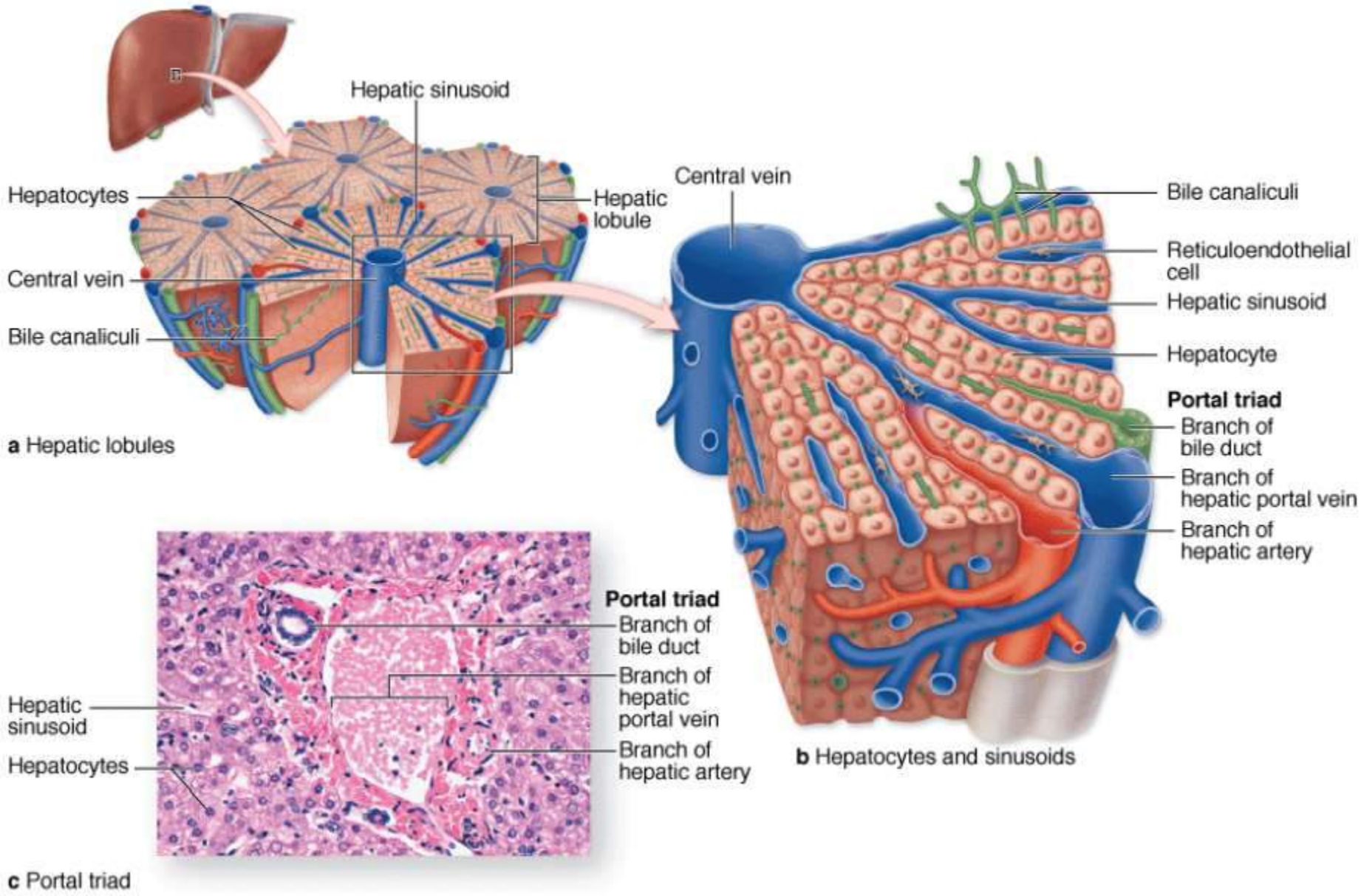
Hepatic veins



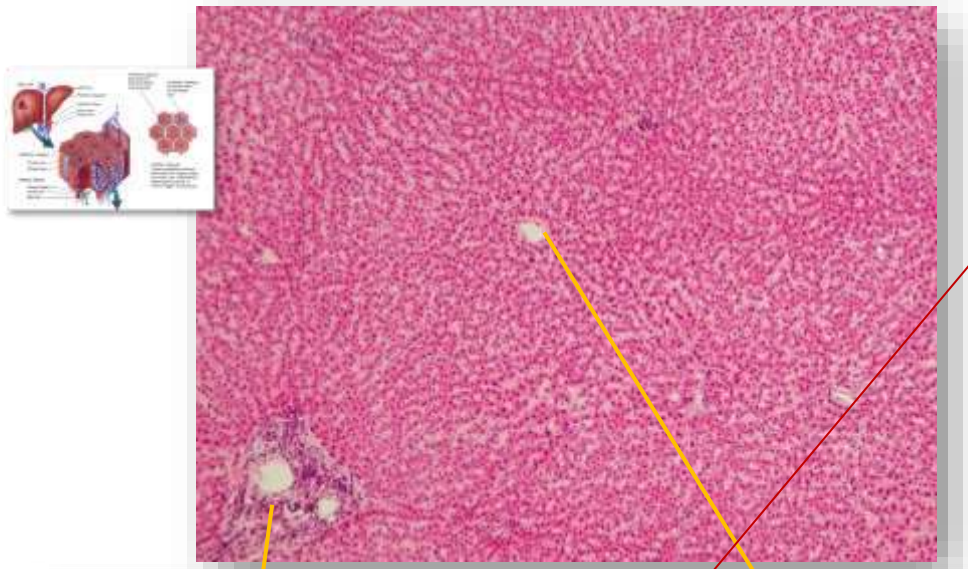


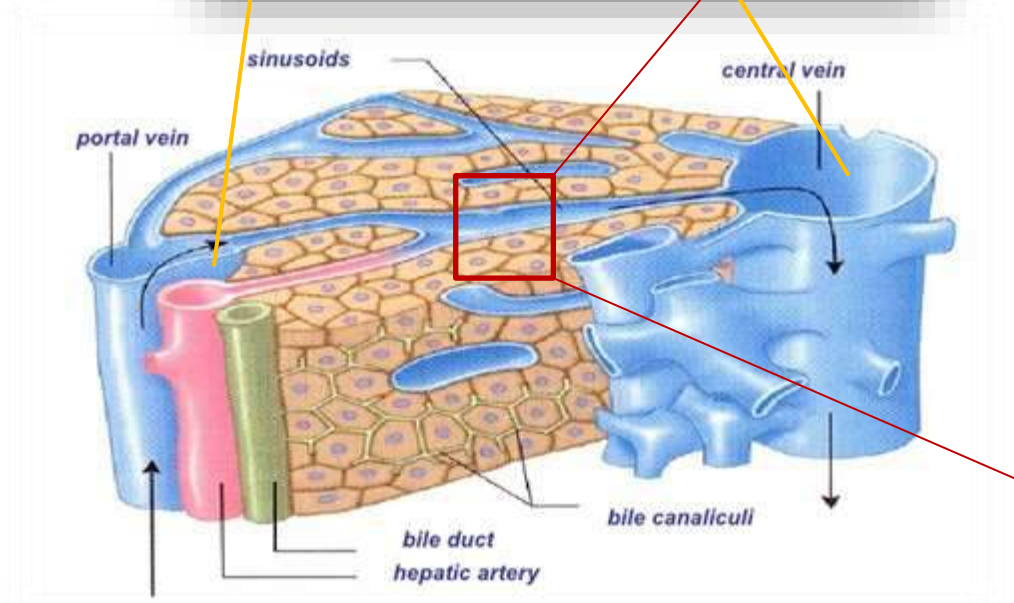


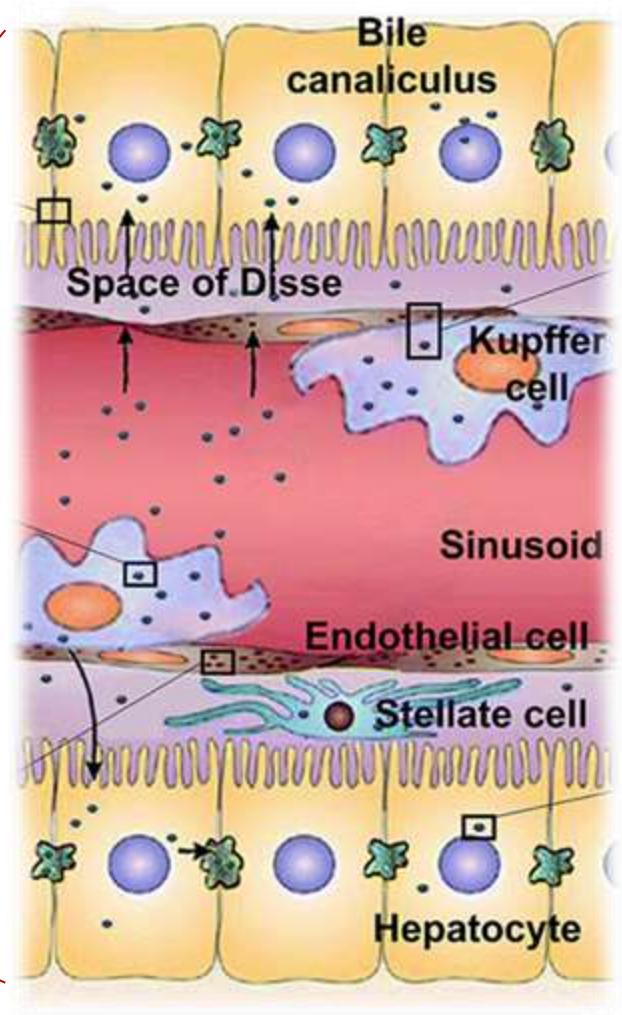



Hepatic sinusoid
Hepatocytes
Hepatic lobule
Central vein
Bile canaliculi
a Hepatic lobules
Central vein
Bile canaliculi
Reticuloendothelial cell
Hepatic sinusoid
Hepatocyte
Portal triad
Branch of bile duct
Branch of hepatic portal vein
Branch of hepatic artery
b Hepatocytes and sinusoids
Portal triad
Branch of bile duct
Branch of hepatic portal vein
Branch of hepatic artery
Hepatic sinusoid
Hepatocytes
c Portal triad

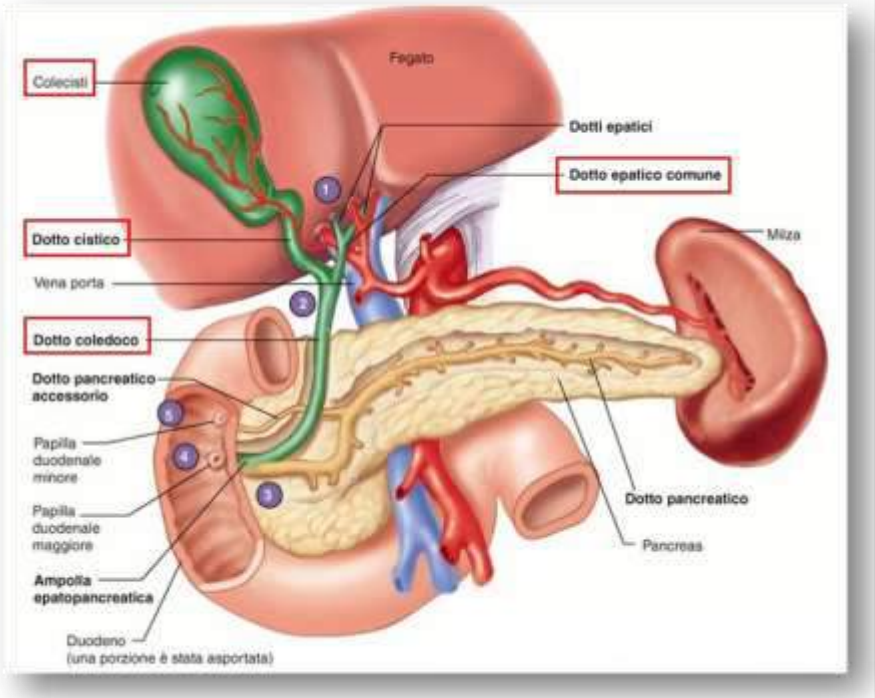
Liver functional anatomy

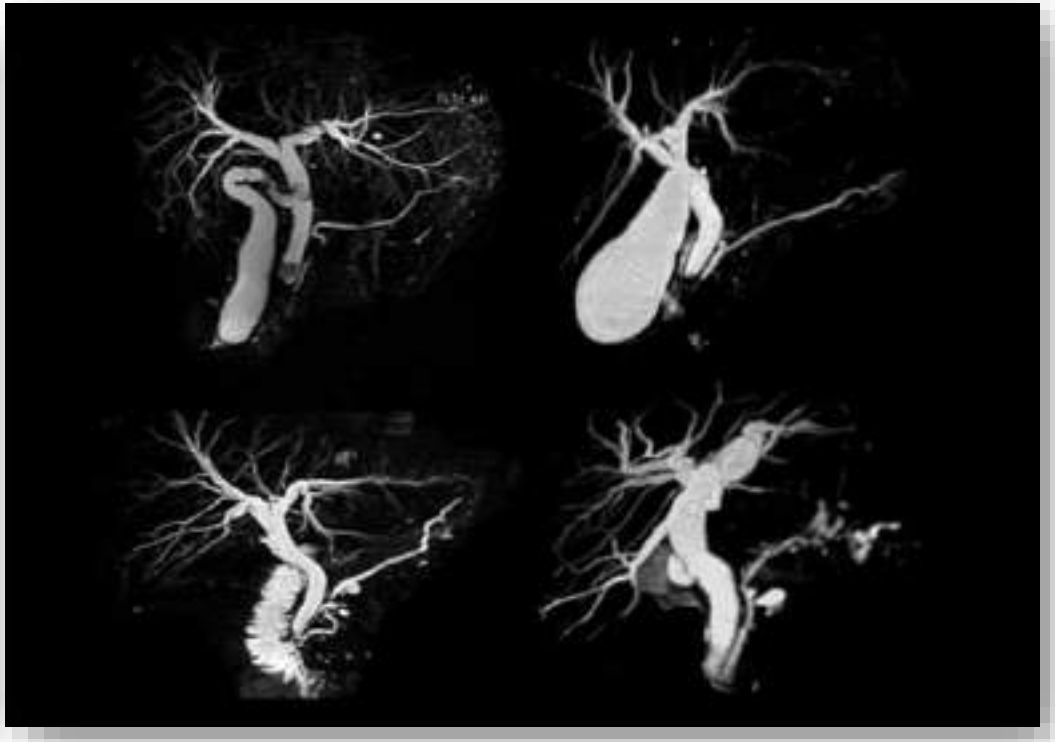




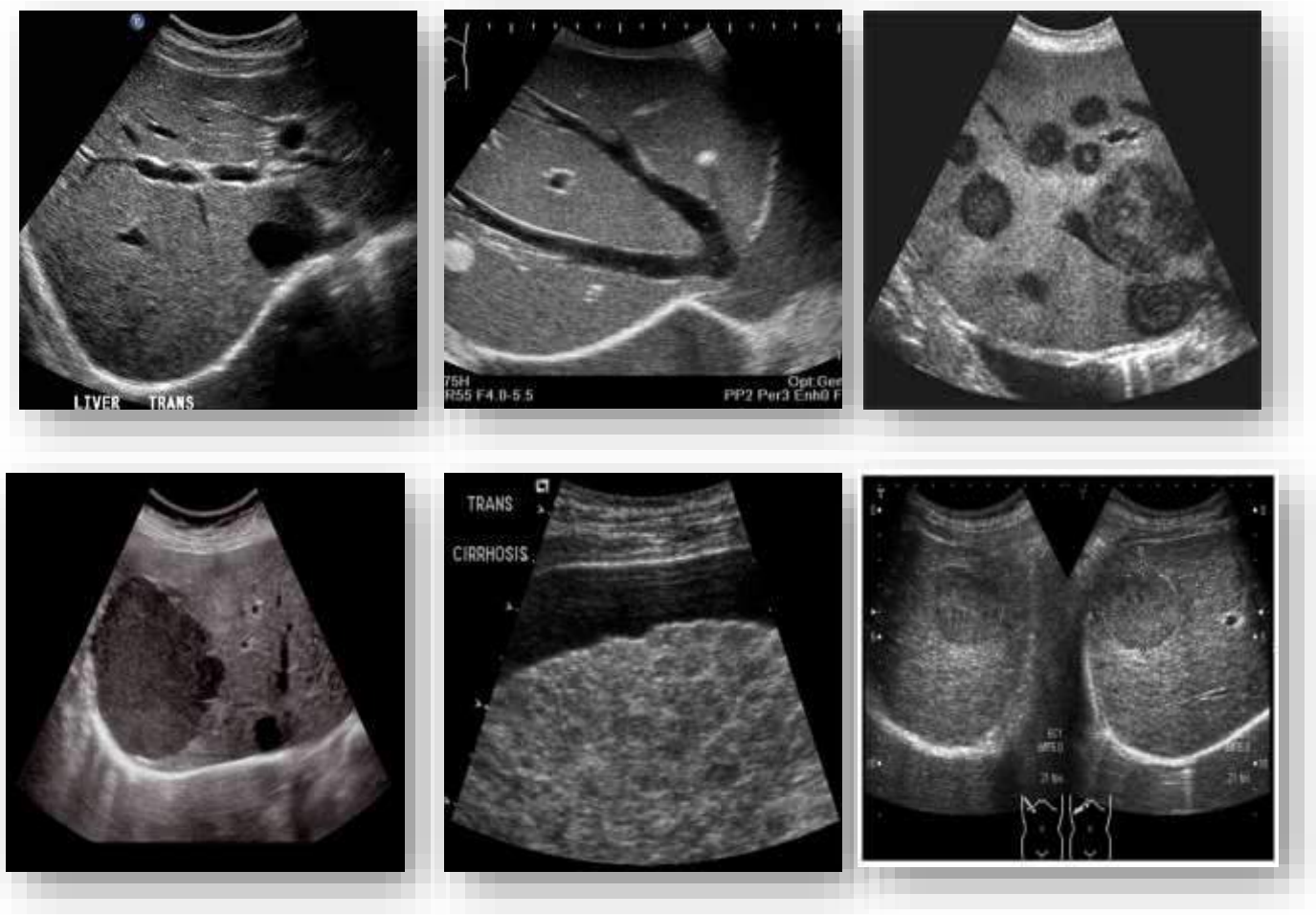


Biliary system
MR and colangio-MR





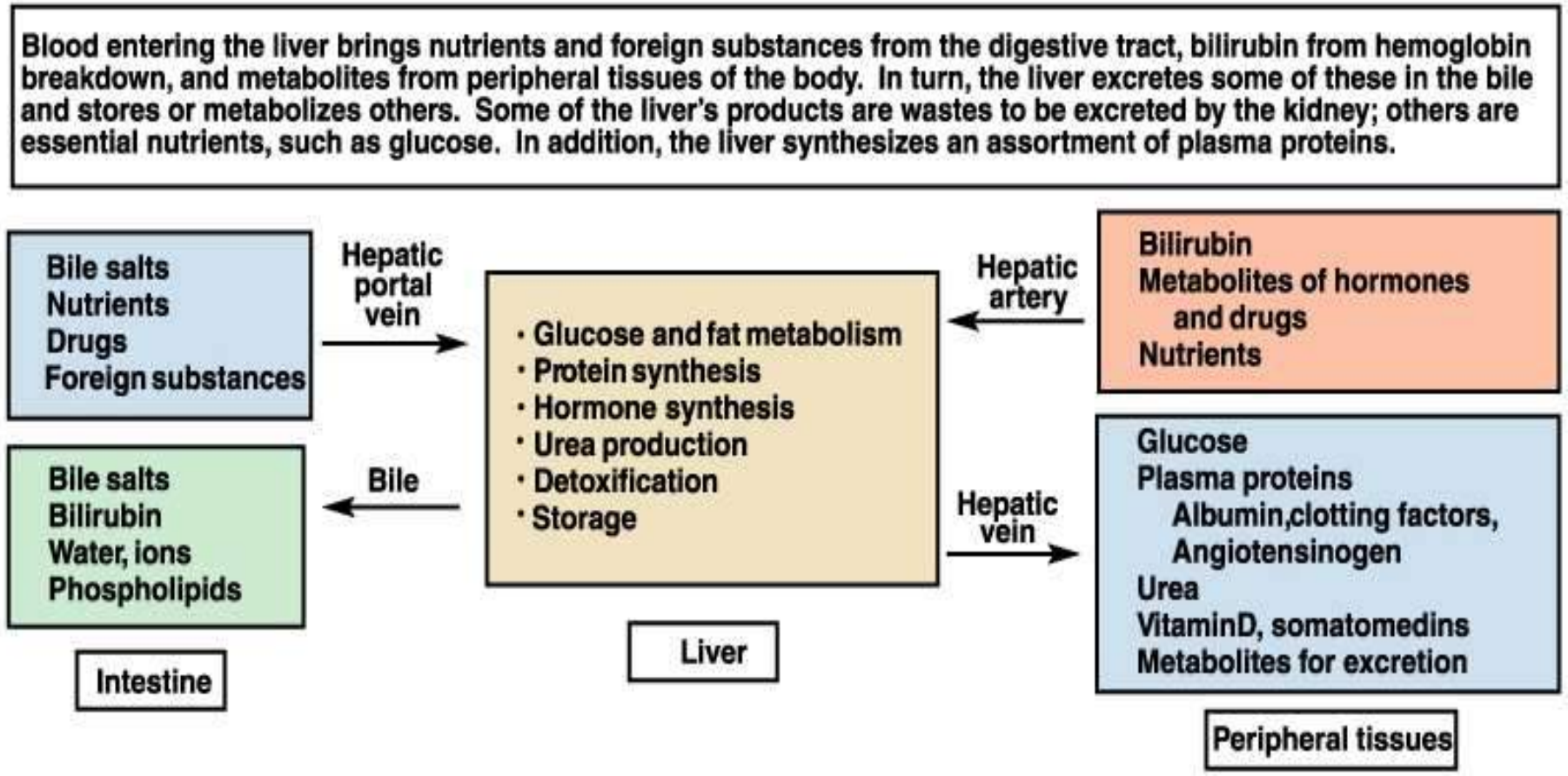
Liver anatomy and pathology: sonography

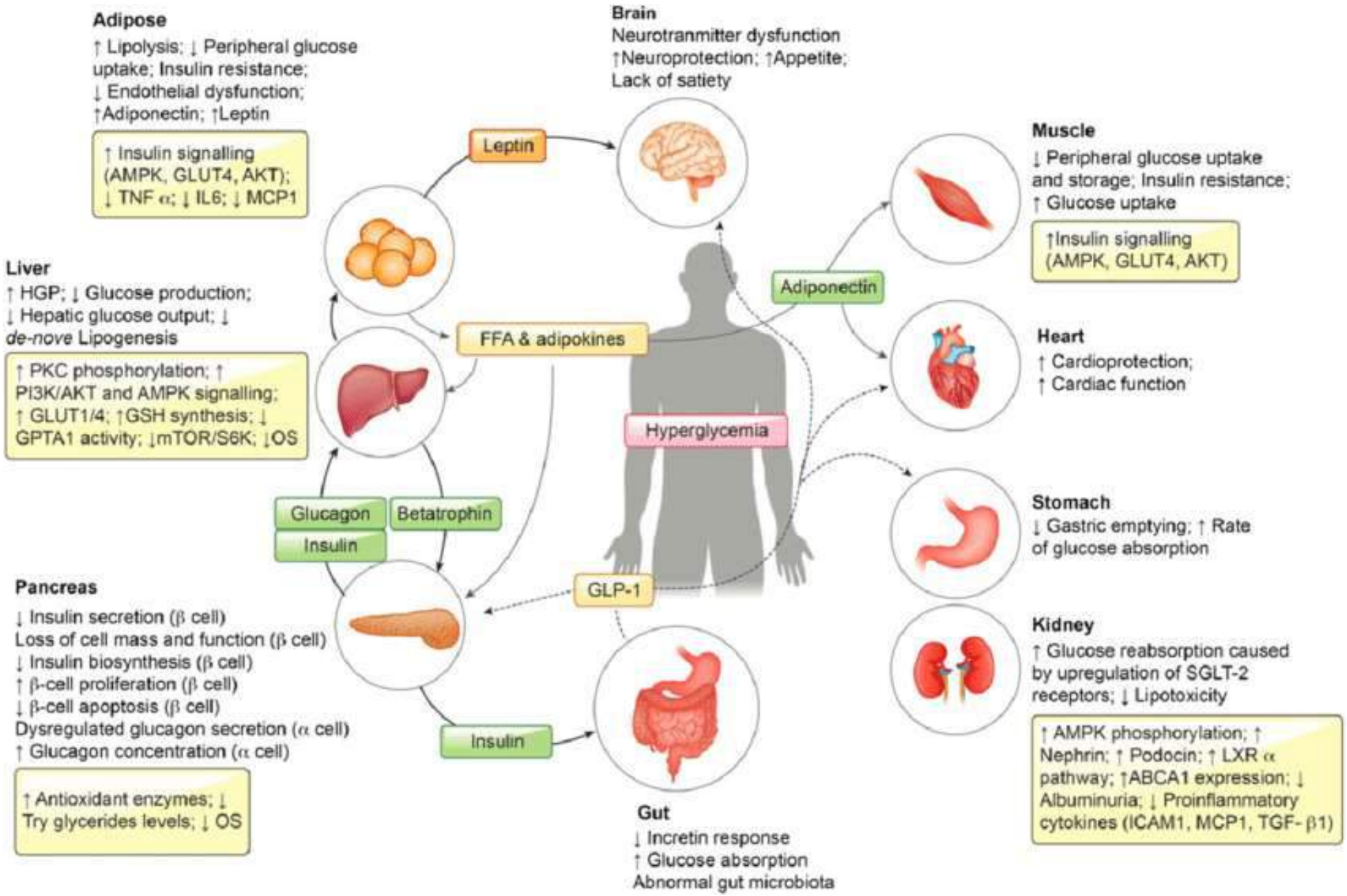


Fiorucci S, Atlante di ecografia in gastroenterologia ed epatologia , 2003

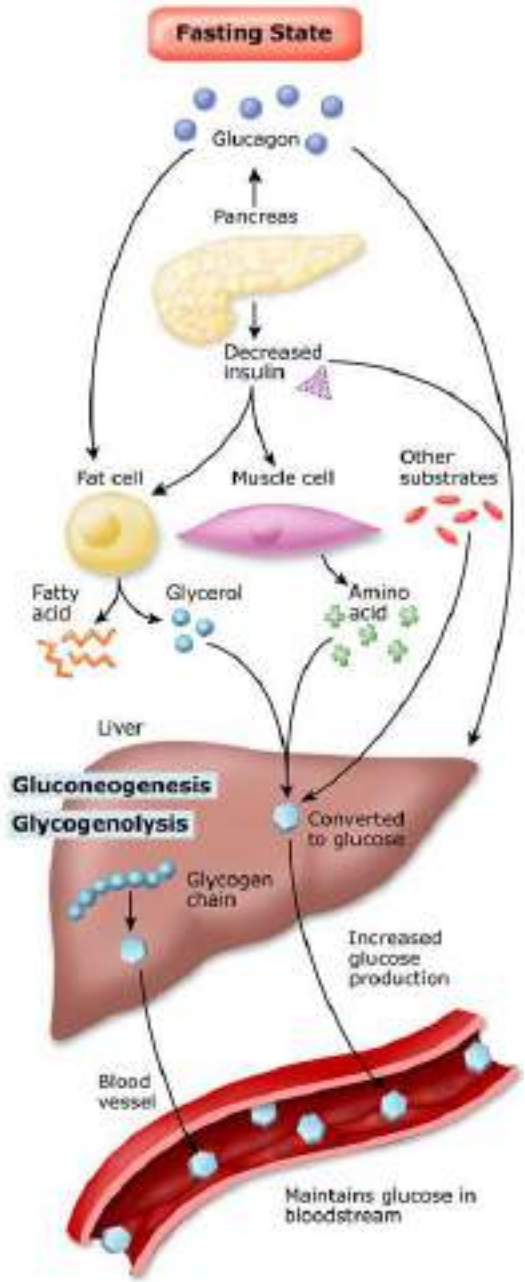
Liver function

Input and Output Pathways of the Liver

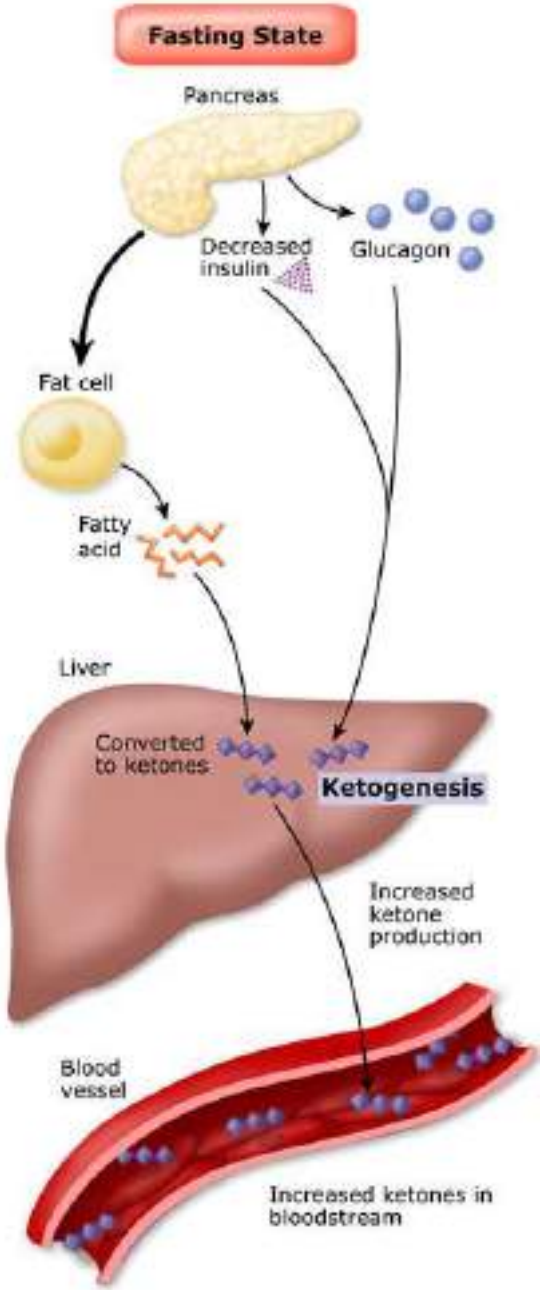


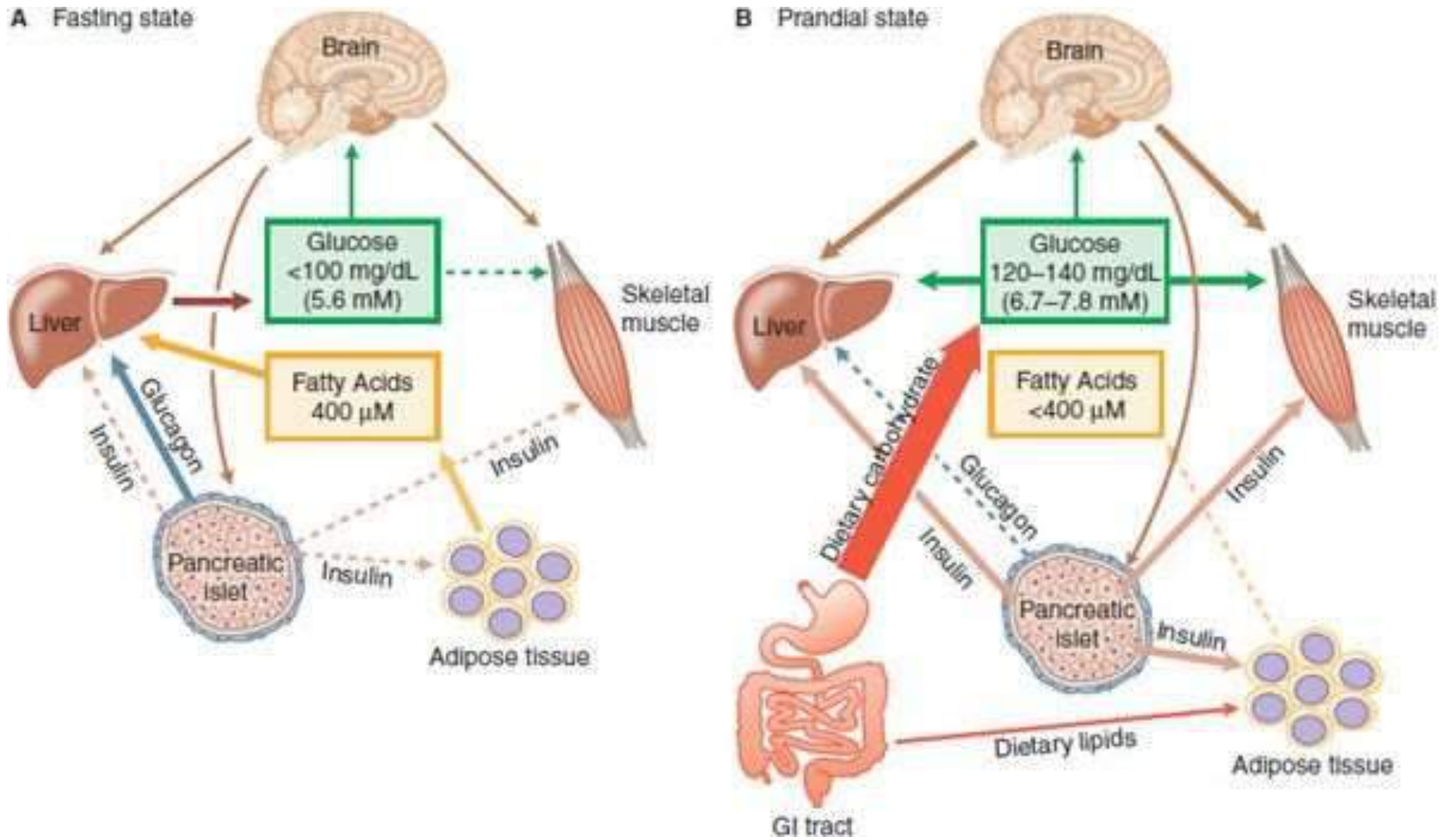

Adipose
↑ Lipolysis; ↓ Peripheral glucose uptake; Insulin resistance; ↓ Endothelial dysfunction; ↑Adiponectin; ↑Leptin
↑ Insulin signalling (AMPK, GLUT4, AKT); ↓ TNF α; ↓ IL6; ↓ MCP1
Brain
Neurotranmitter dysfunction
↑Neuroprotection; ↑Appetite; Lack of satiety
Leptin
Muscle
↓ Peripheral glucose uptake and storage; Insulin resistance; ↑ Glucose uptake
↑Insulin signalling (AMPK, GLUT4, AKT)
Liver
↑ HGP; ↓ Glucose production; ↓ Hepatic glucose output; ↓ de-nove Lipogenesis
↑ PKC phosphorylation; ↑ PI3K/AKT and AMPK signalling; ↑ GLUT1/4; ↑GSH synthesis; ↓ GPTA1 activity; ↓mTOR/S6K; ↓OS
FFA & adipokines
Adiponectin
Heart
↑ Cardioprotection; ↑ Cardiac function
Hyperglycemia
Glucagon
Betatrophin
Insulin
Stomach
↓ Gastric emptying; ↑ Rate of glucose absorption
Pancreas
↓ Insulin secretion (β cell)
Loss of cell mass and function (β cell)
↓ Insulin biosynthesis (β cell)
↑ β-cell proliferation (β cell)
↓ β-cell apoptosis (β cell)
Dysregulated glucagon secretion (α cell)
↑ Glucagon concentration (α cell)
↑ Antioxidant enzymes; ↓ Try glycerides levels; ↓ OS
GLP-1
Kidney
↑ Glucose reabsorption caused by upregulation of SGLT-2 receptors; ↓ Lipotoxicity
↑ AMPK phosphorylation; ↑ Nephrin; ↑ Podocin; ↑ LXR α pathway; ↑ABCA1 expression; ↓ Albuminuria; ↓ Proinflammatory cytokines (ICAM1, MCP1, TGF- β1)
Insulin
Gut
↓ Incretin response
↑ Glucose absorption
Abnormal gut microbiota

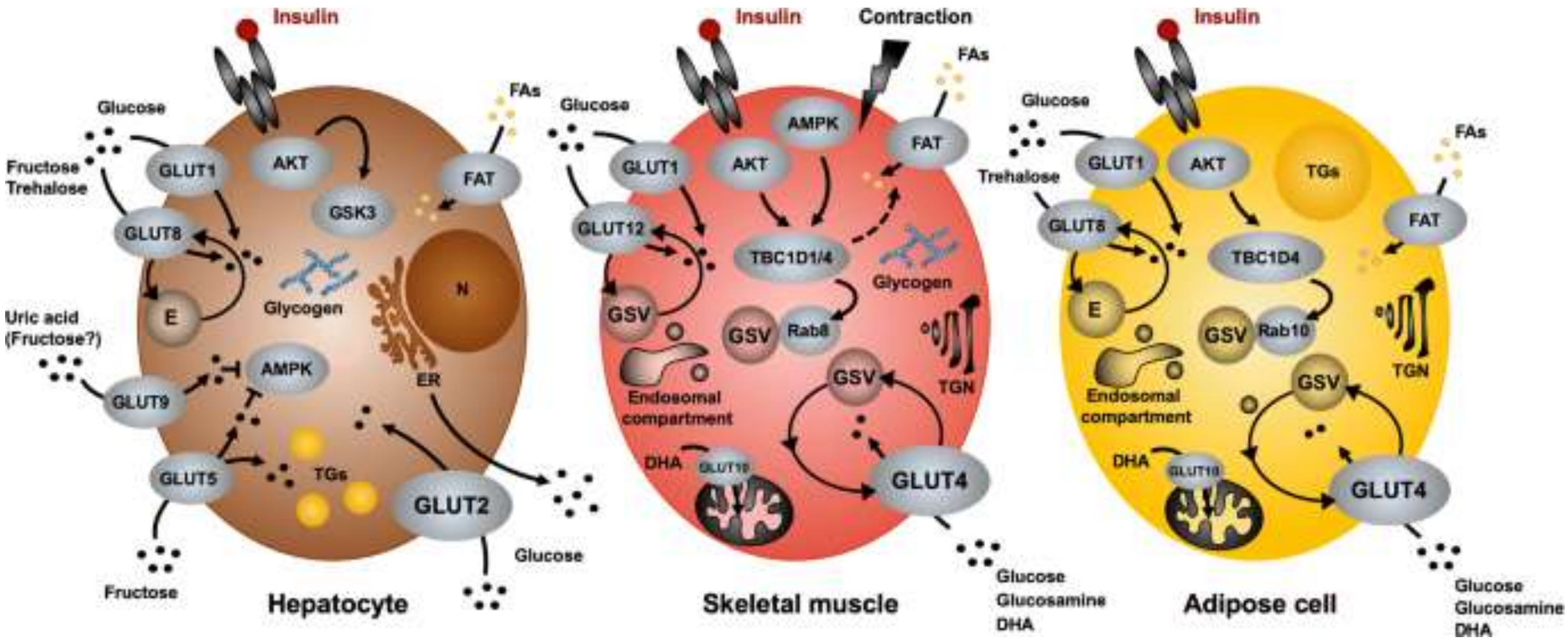
Glucose Production by Liver During Fasting Conditions (Gluconeogenesis and Glycogenolysis)

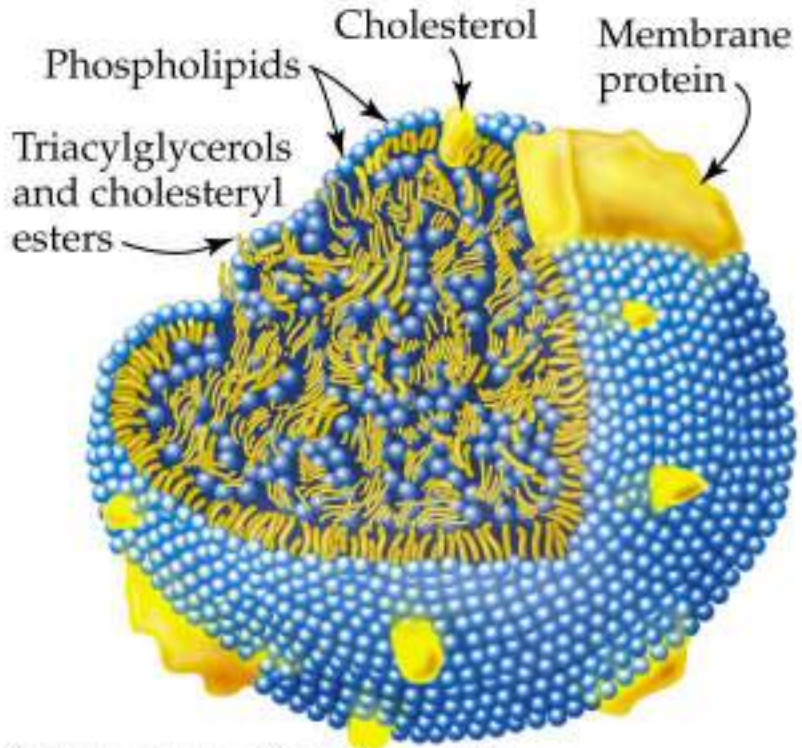


Ketone Production by Liver During Fasting Conditions (Ketosis)

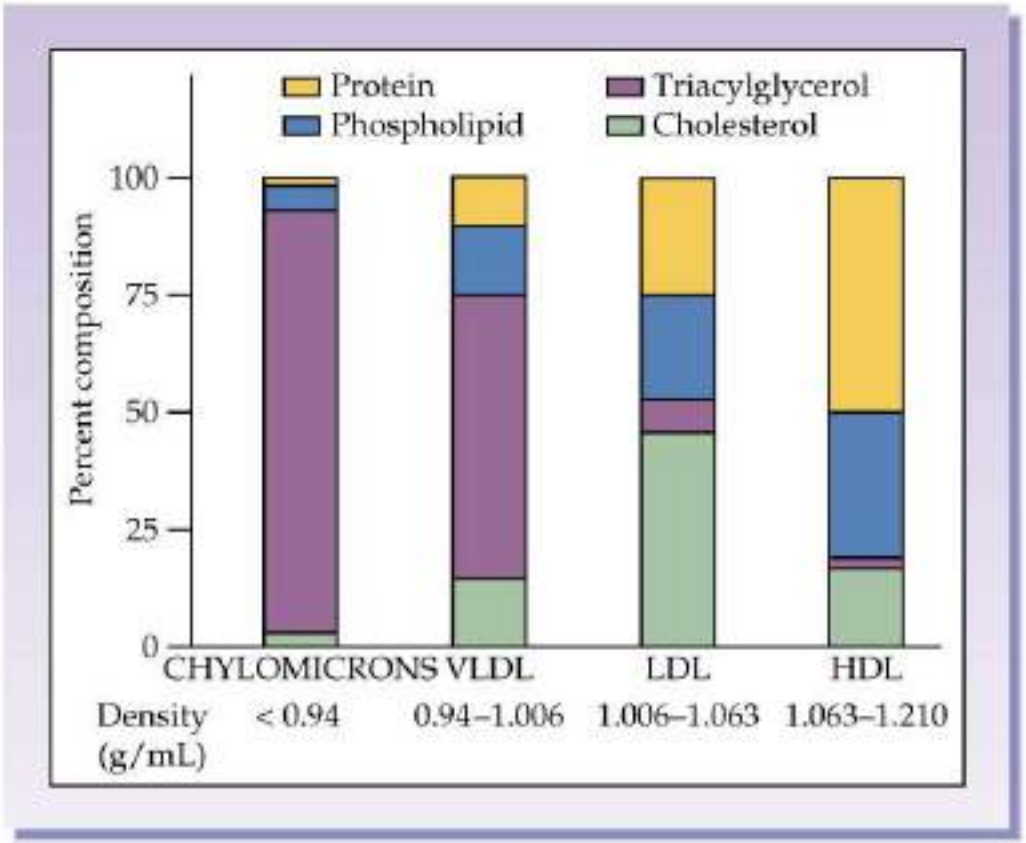



A Fasting state
Brain
Glucose
<100 mg/dL
(5.6 mM)
Liver
Skeletal
muscle
Fatty Acids
400 µM
Glucagon
Insulin
Insulin
Pancreatic
islet
Insulin
Adipose tissue
B Prandial state
Brain
Glucose
120–140 mg/dL
(6.7–7.8 mM)
Liver
Skeletal
muscle
Fatty Acids
<400 µM
Dietary carbohydrate
Glucagon
Insulin
Insulin
Pancreatic
islet
Insulin
Dietary lipids
Adipose tissue
GI tract

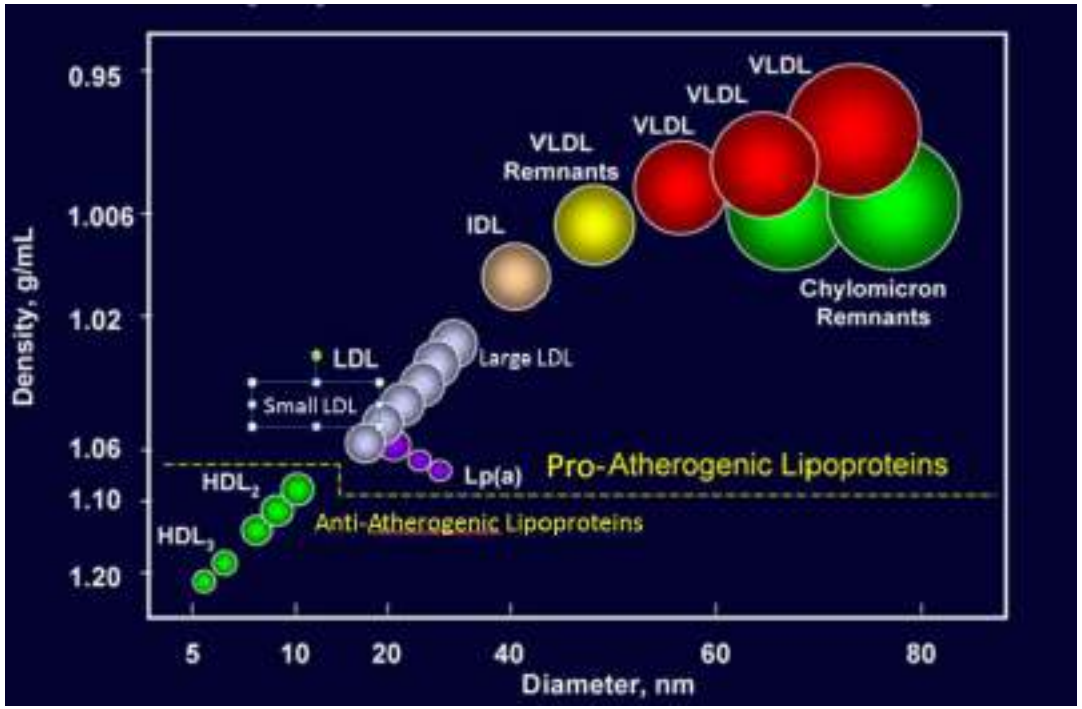

Insulin
Glucose
Fructose
Trehalose
GLUT1
AKT
GSK3
FAs
FAT
GLUT8
E
Glycogen
N
Uric acid
(Fructose?)
AMPK
GLUT9
ER
GLUT5
TGs
GLUT2
Glucose
Fructose
Hepatocyte
Insulin
Contraction
Glucose
FAs
AMPK
FAT
GLUT1
AKT
GLUT12
TBC1D1/4
Glycogen
GSV
GSV
Rab8
TGN
GSV
Endosomal
compartment
DHA
GLUT10
GLUT4
Glucose
Glucosamine
DHA
Skeletal muscle
Insulin
Glucose
Trehalose
GLUT1
AKT
TGs
FAs
GLUT8
TBC1D4
FAT
E
GSV
Rab10
TGN
GSV
Endosomal
compartment
DHA
GLUT10
GLUT4
Glucose
Glucosamine
DHA
Adipose cell

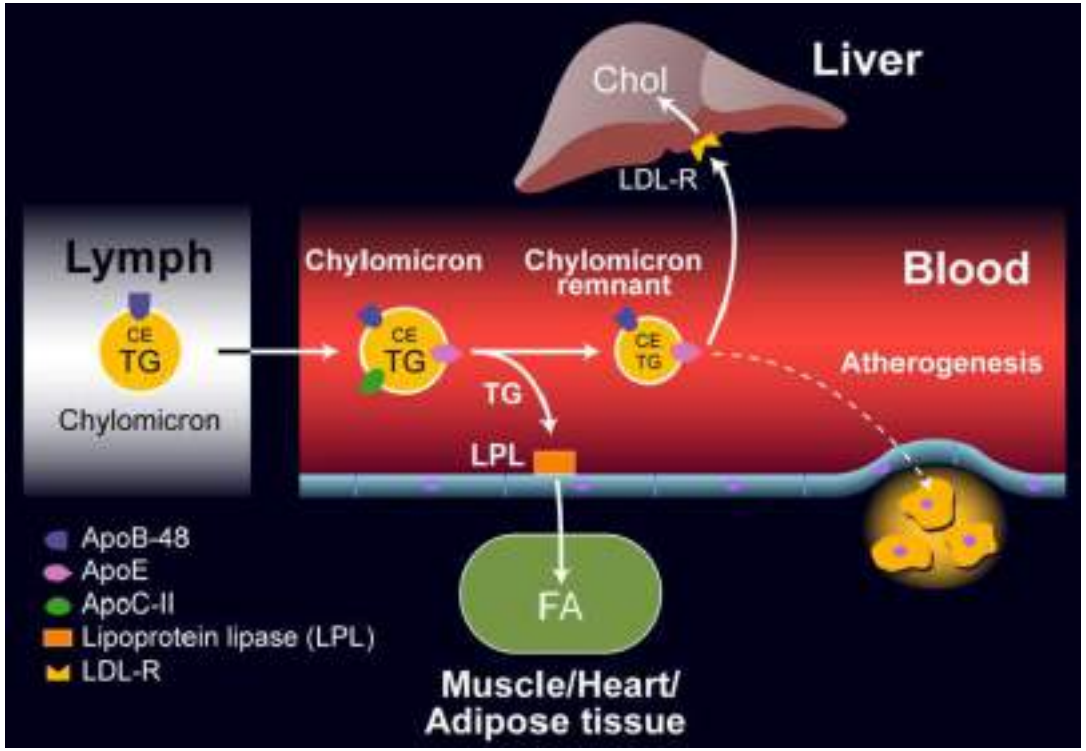


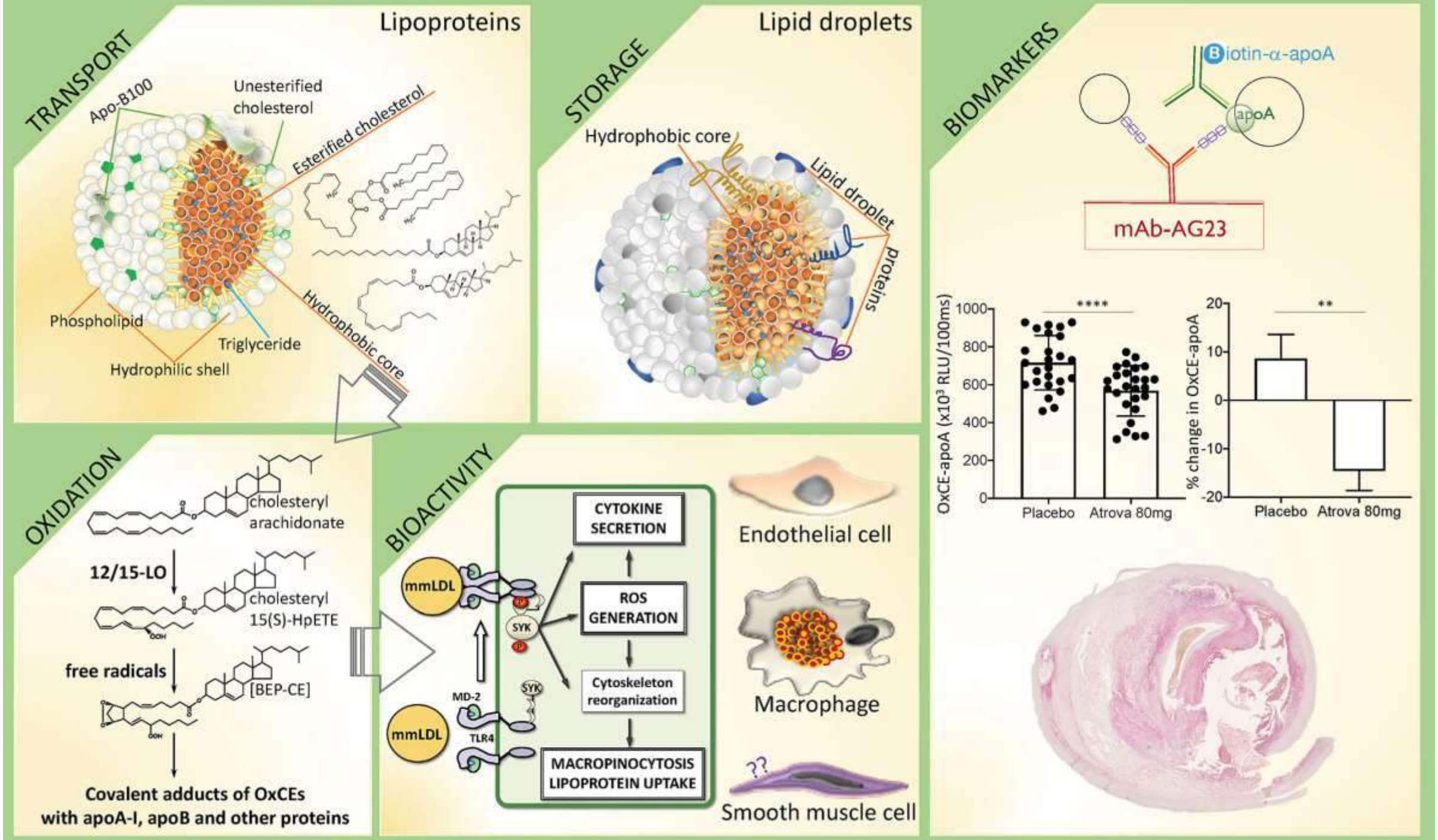
(a) Structure of a lipoprotein

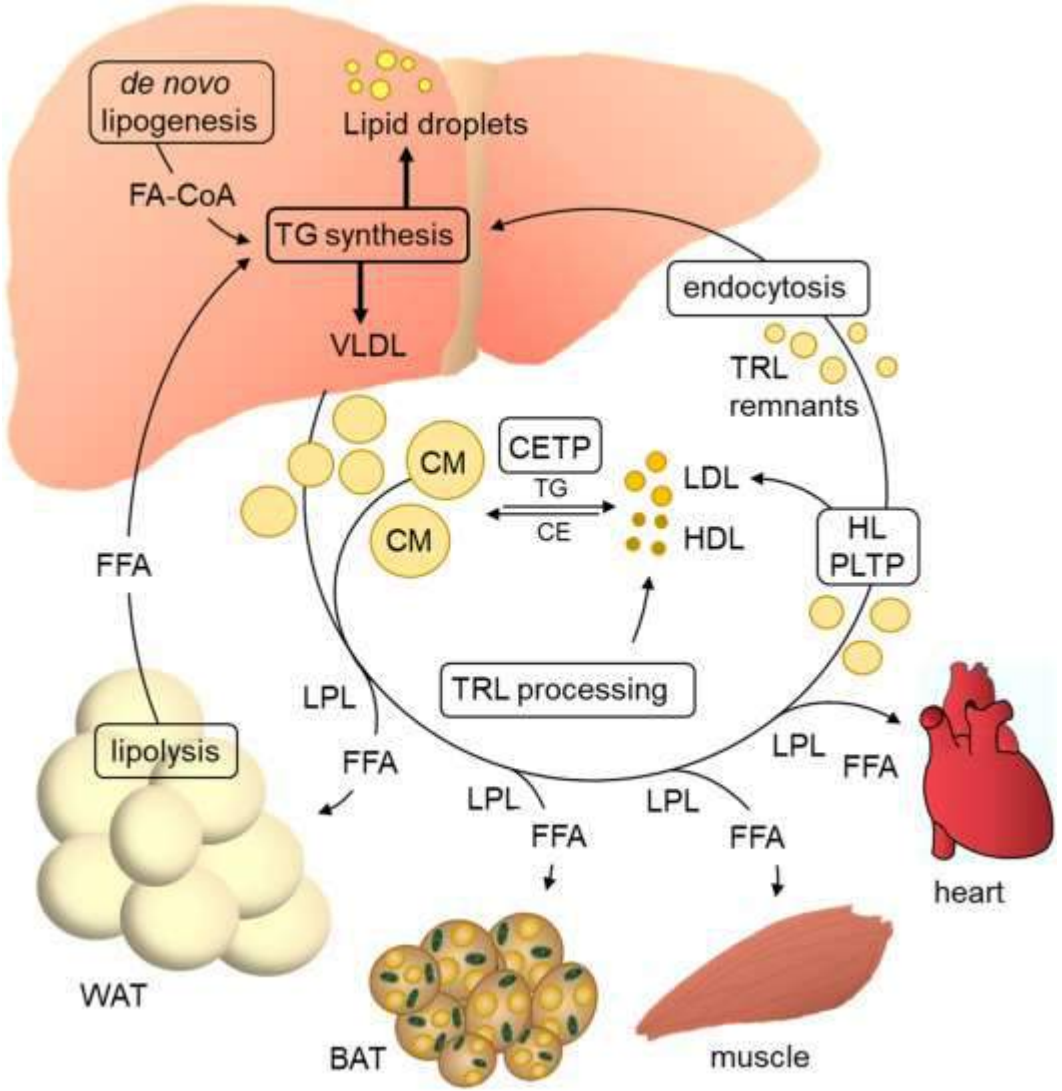


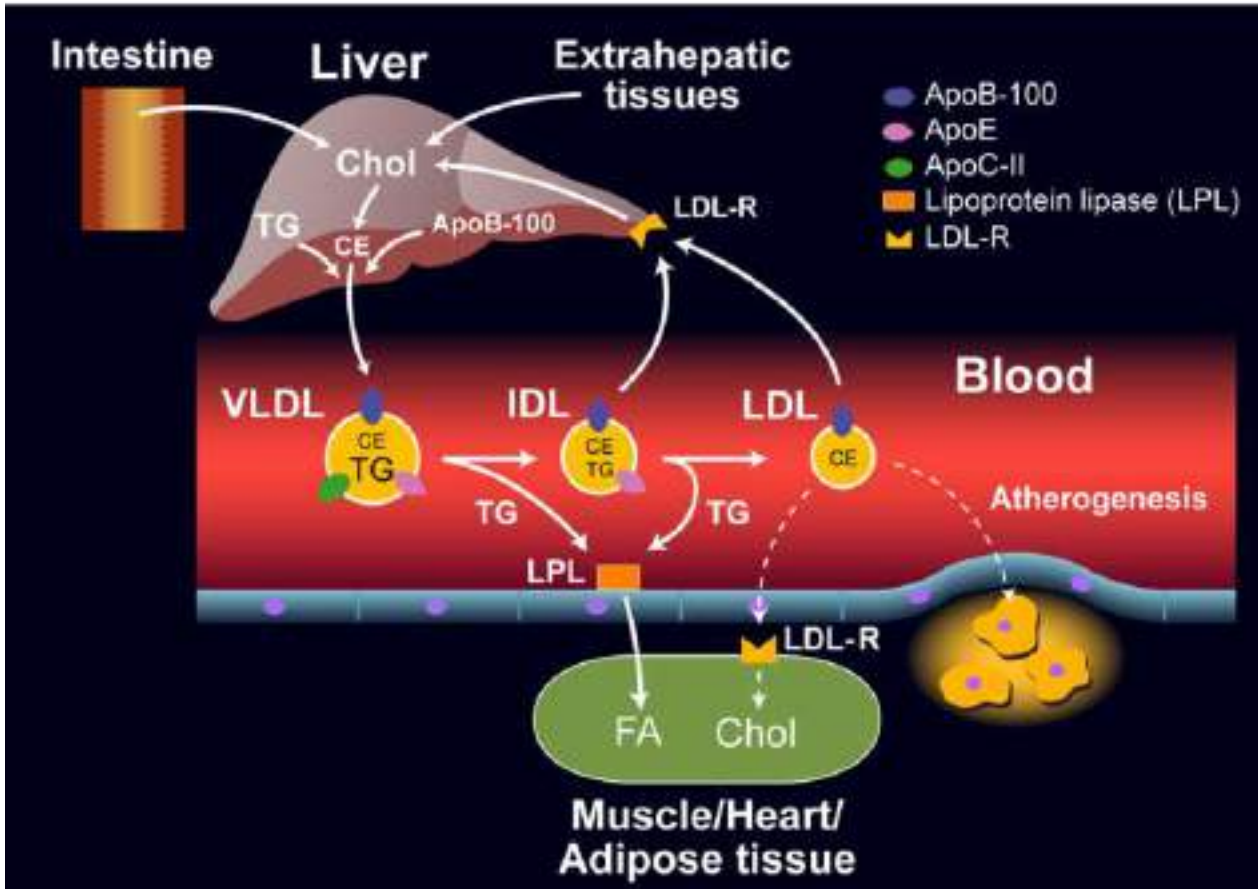
(b) Density and composition of lipoproteins

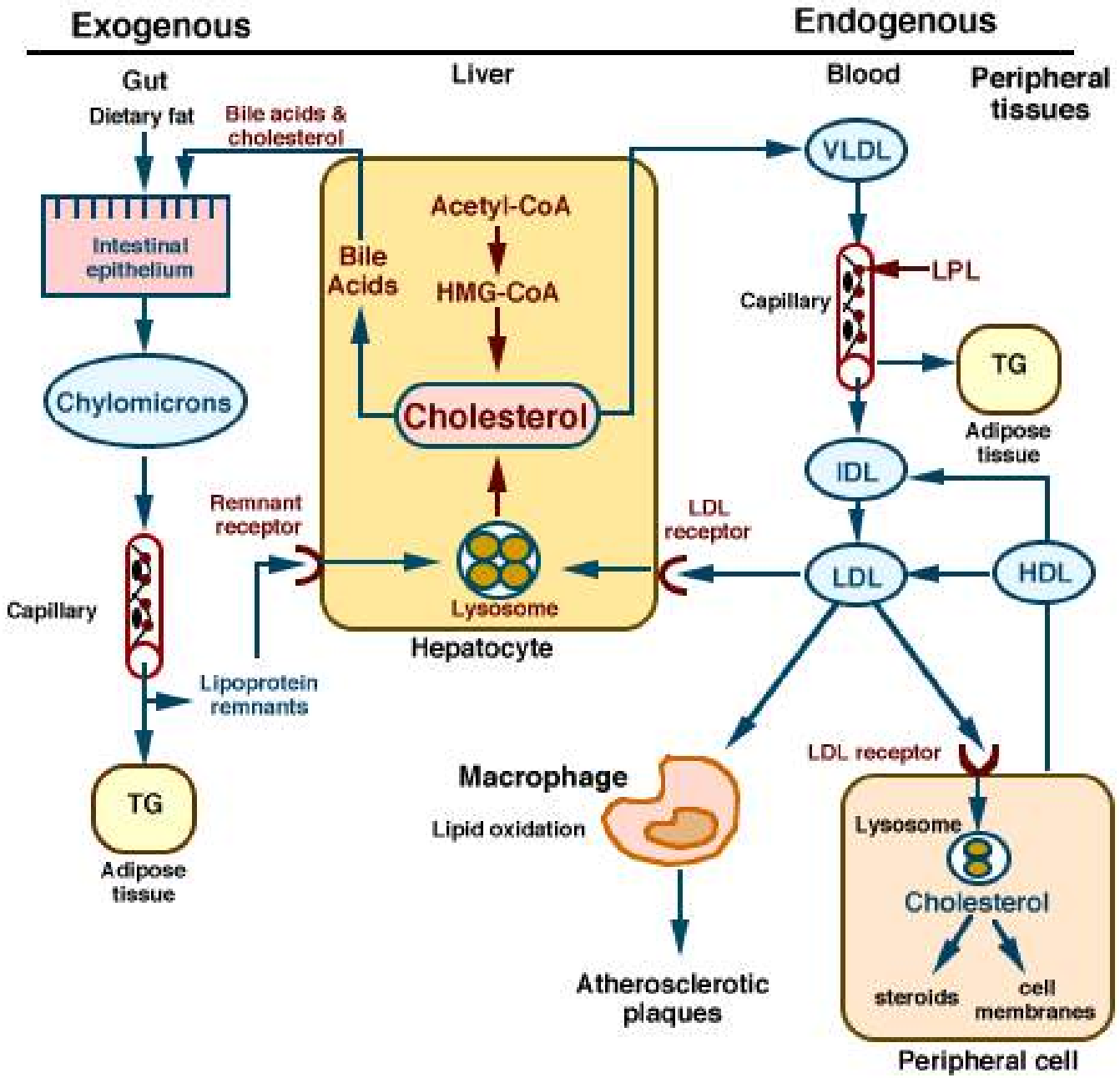

Density, g/mL
0.95
1.006
1.02
1.06
1.10
1.20
5
10
20
40
60
80
Diameter, nm
VLDL
VLDL
VLDL
VLDL Remnants
IDL
Chylomicron Remnants
LDL
Large LDL
Small LDL
Lp(a)
Pro-Atherogenic Lipoproteins
HDL2
HDL3
Anti-Atherogenic Lipoproteins


Liver
Chol
LDL-R
Lymph
CE
TG
Chylomicron
Chylomicron
Chylomicron remnant
Blood
Atherogenesis
TG
LPL
FA
ApoB-48
ApoE
ApoC-II
Lipoprotein lipase (LPL)
LDL-R
Muscle/Heart/
Adipose tissue

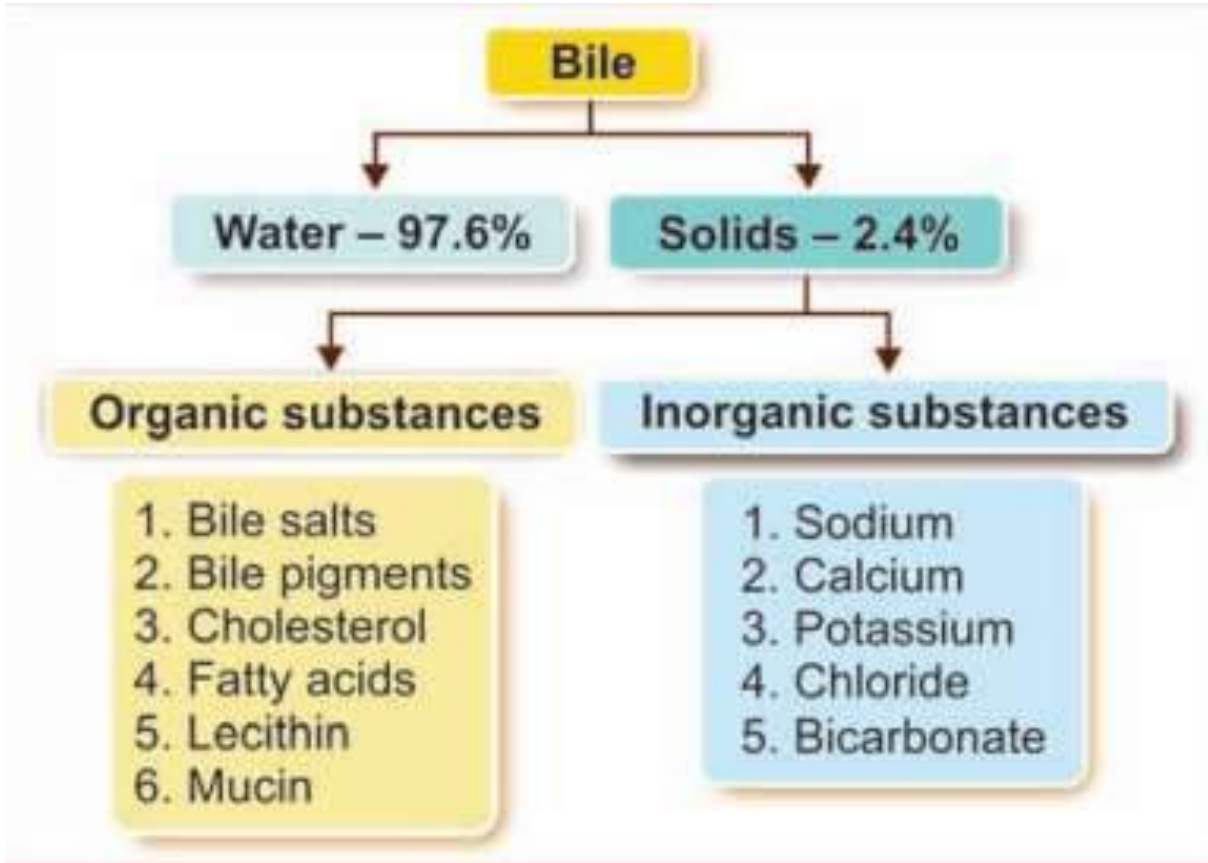

TRANSPORT
Lipoproteins
Apo-B100
Unesterified cholesterol
Esterified cholesterol
Phospholipid
Triglyceride
Hydrophilic shell
Hydrophobic core
STORAGE
Lipid droplets
Hydrophobic core
Lipid droplet proteins
BIOMARKERS
Biotin-α-apoA
apoA
mAb-AG23
OxCE-apoA (x10³ RLU/100ms)
1000
800
600
400
200
0
****
Placebo
Atrova 80mg
% change in OxCE-apoA
20
10
0
-10
-20
**
Placebo
Atrova 80mg
OXIDATION
cholesteryl arachidonate
12/15-LO
cholesteryl 15(S)-HpETE
free radicals
[BEP-CE]
Covalent adducts of OxCEs with apoA-I, apoB and other proteins
BIOACTIVITY
mmLDL
mmLDL
MD-2
TLR4
SYK
SYK
CYTOKINE SECRETION
ROS GENERATION
Cytoskeleton reorganization
MACROPINOCYTOSIS LIPOPROTEIN UPTAKE
Endothelial cell
Macrophage
??
Smooth muscle cell

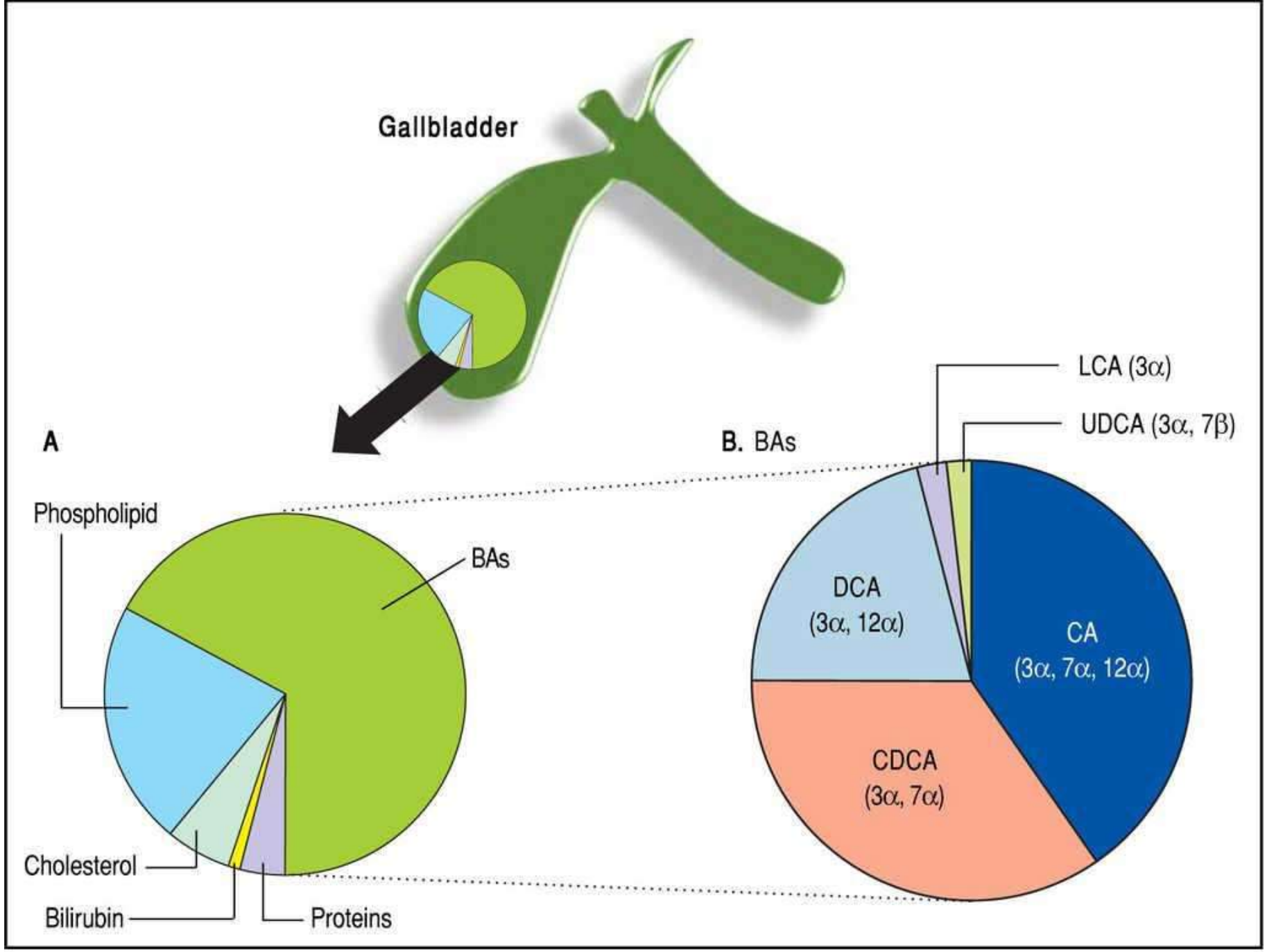

de novo lipogenesis
Lipid droplets
FA-CoA
TG synthesis
VLDL
endocytosis
TRL remnants
CM
CM
CETP
TG
CE
LDL
HDL
HL PLTP
FFA
TRL processing
LPL
FFA
LPL
FFA
LPL
FFA
LPL
FFA
lipolysis
WAT
BAT
muscle
heart


Intestine
Liver
Extrahepatic tissues
ApoB-100
ApoE
ApoC-II
Lipoprotein lipase (LPL)
LDL-R
Chol
TG
CE
ApoB-100
LDL-R
Blood
VLDL
IDL
LDL
CE
TG
CE
TG
CE
TG
TG
Atherogenesis
LPL
LDL-R
FA
Chol
Muscle/Heart/
Adipose tissue

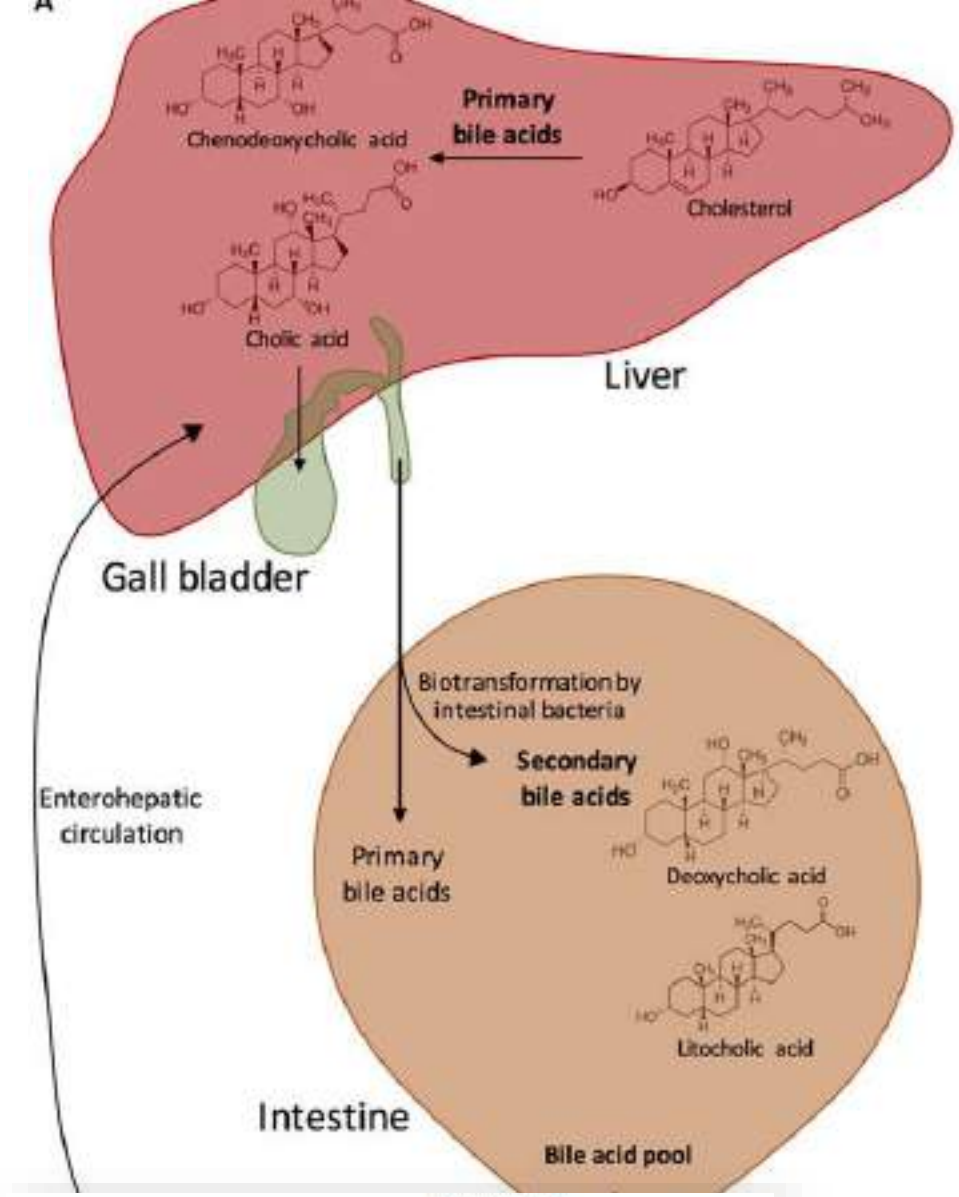

Exogenous
Endogenous
Gut
Liver
Blood
Peripheral tissues
Dietary fat
Bile acids & cholesterol
Intestinal epithelium
Chylomicrons
Capillary
TG
Adipose tissue
Lipoprotein remnants
Remnant receptor
Acetyl-CoA
HMG-CoA
Bile Acids
Cholesterol
Lysosome
Hepatocyte
LDL receptor
VLDL
LPL
Capillary
TG
Adipose tissue
IDL
LDL
HDL
Macrophage
Lipid oxidation
Atherosclerotic plaques
LDL receptor
Lysosome
Cholesterol
steroids
cell membranes
Peripheral cell

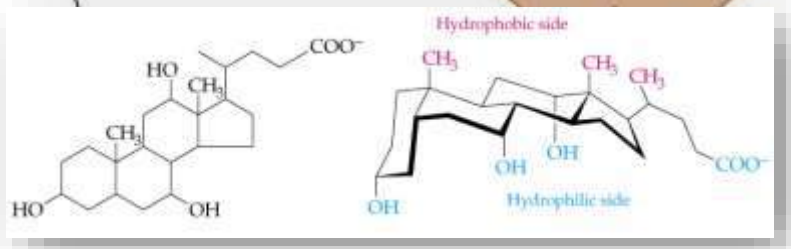
Bile acids

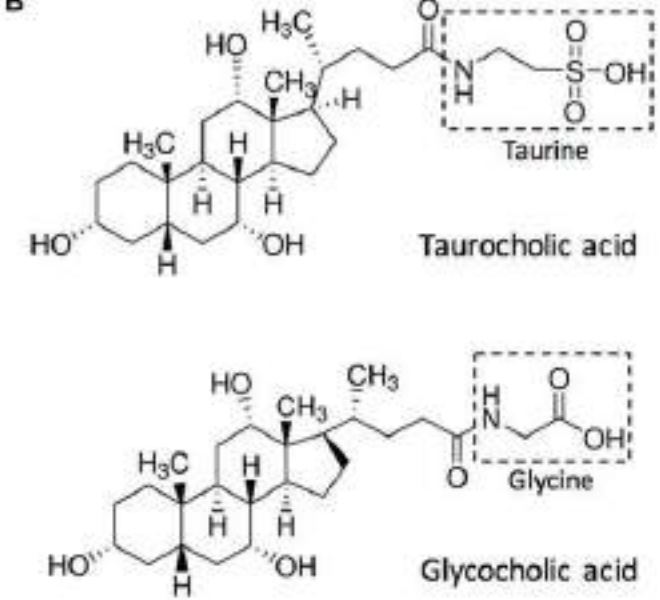

Bile
Water – 97.6%
Solids – 2.4%
Organic substances
1. Bile salts
2. Bile pigments
3. Cholesterol
4. Fatty acids
5. Lecithin
6. Mucin
Inorganic substances
1. Sodium
2. Calcium
3. Potassium
4. Chloride
5. Bicarbonate

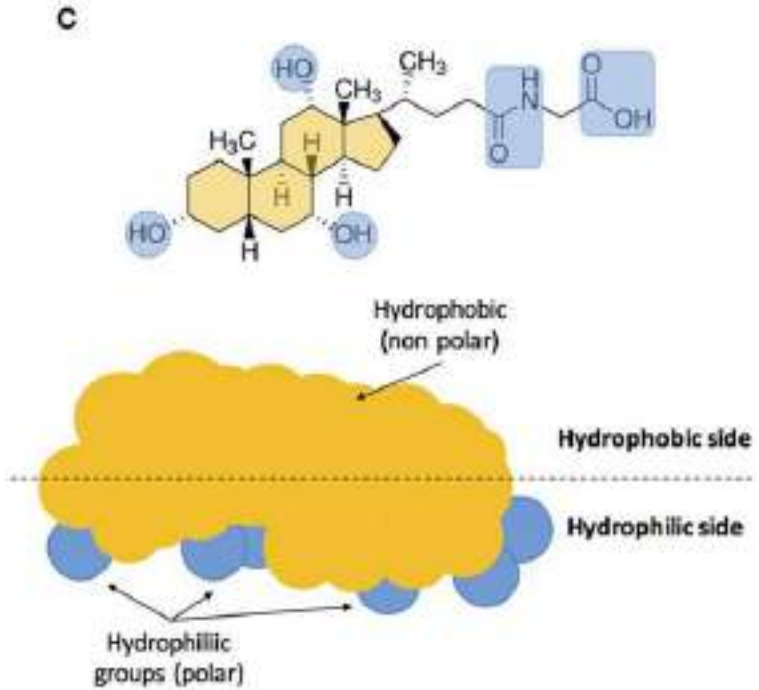


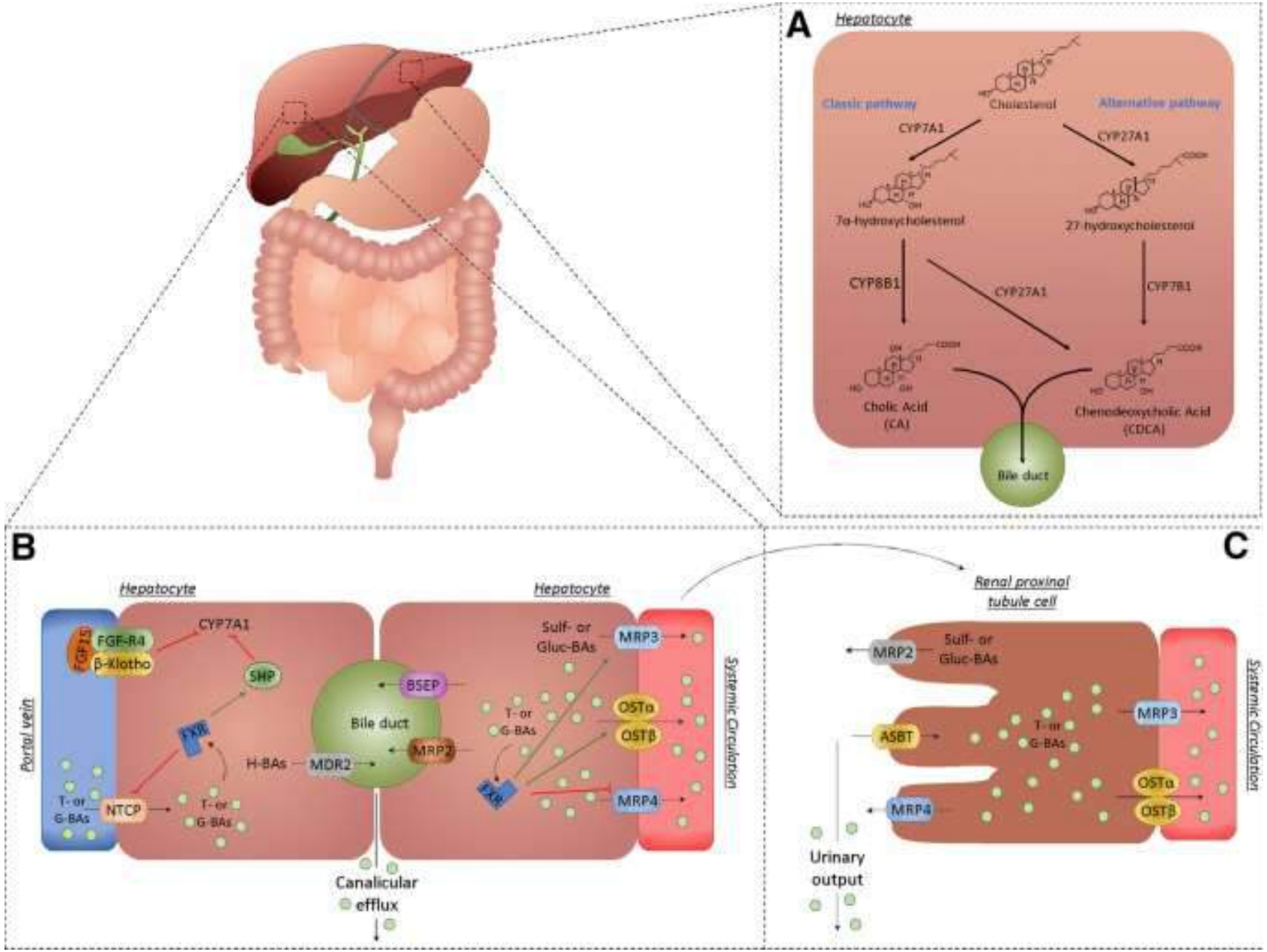
Ann Hepatol. 2017;16 Supl 1:S4–S14

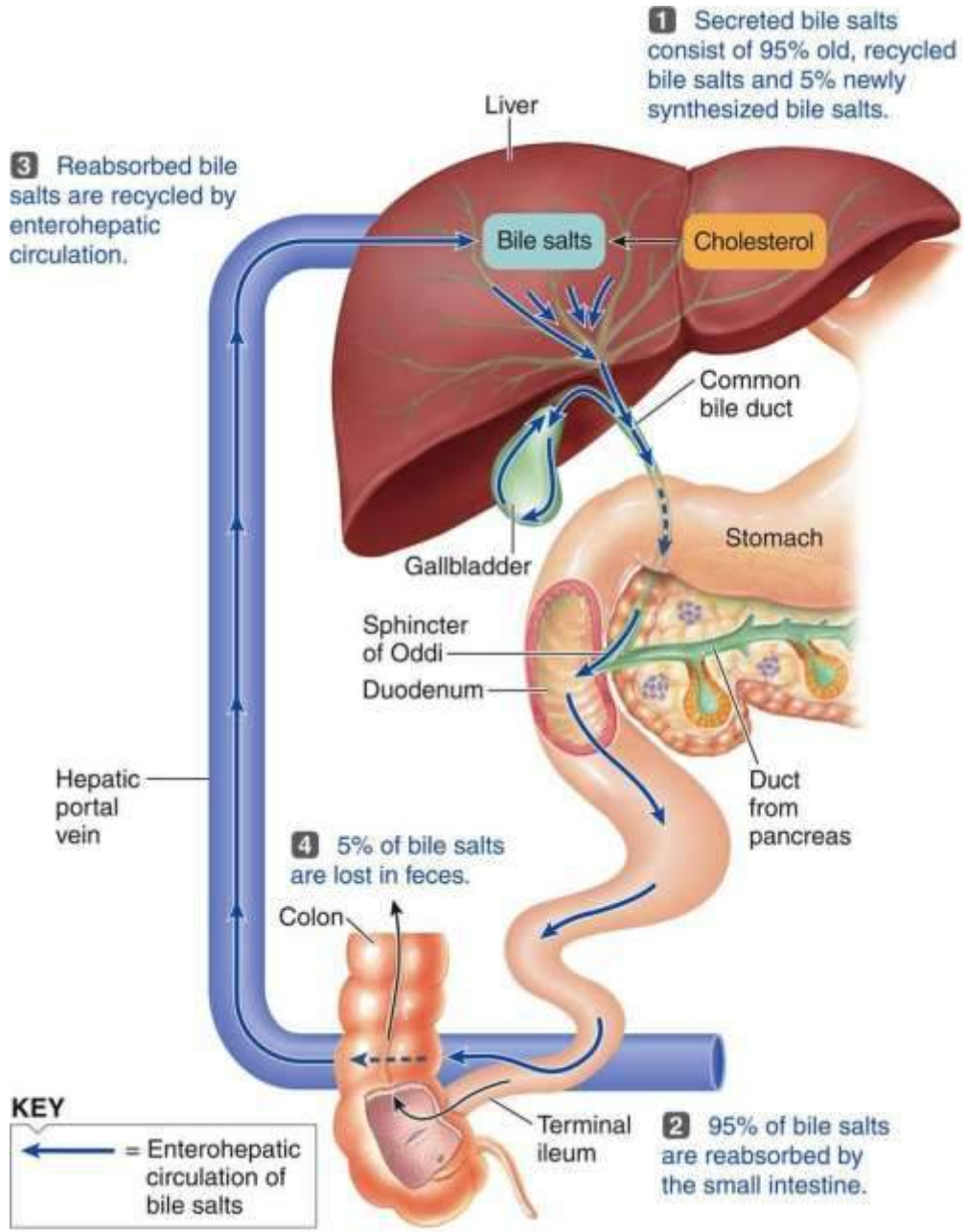

A
Chenodeoxycholic acid
Primary bile acids
Cholesterol
Cholic acid
Liver
Gall bladder
Biotransformation by intestinal bacteria
Secondary bile acids
Enterohepatic circulation
Primary bile acids
Deoxycholic acid
Litocholic acid
Intestine
Bile acid pool

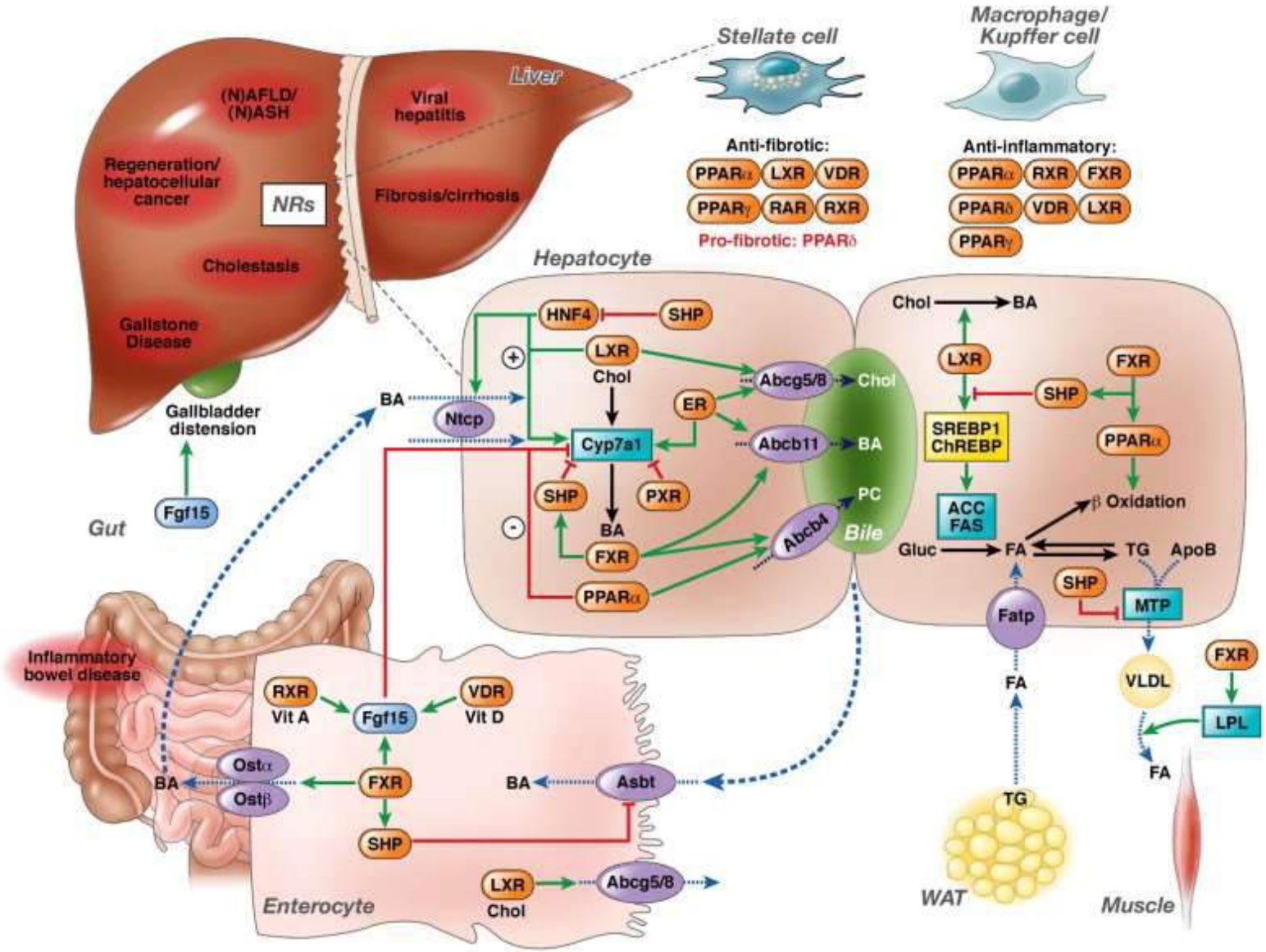

Hydrophobic side
Hydrophilic side


B
Taurine
Taurocholic acid
Glycine
Glycocholic acid


C
Hydrophobic (non polar)
Hydrophobic side
Hydrophilic side
Hydrophillic groups (polar)


A
Hepatocyte
Classic pathway
Cholesterol
Alternative pathway
CYP7A1
CYP27A1
7α-hydroxycholesterol
27-hydroxycholesterol
CYP8B1
CYP27A1
CYP7B1
Cholic Acid (CA)
Chenodeoxycholic Acid (CDCA)
Bile duct
B
Hepatocyte
Hepatocyte
Portal vein
FGF19
FGF-R4
β-Klotho
CYP7A1
SHP
FXR
NTCP
T- or G-BAs
T- or G-BAs
H-BAs
MDR2
BSEP
Bile duct
MRP2
Sulf- or Gluc-BAs
MRP3
OSTα
OSTβ
MRP4
T- or G-BAs
FXR
Systemic Circulation
Canalicular efflux
C
Renal proximal tubule cell
MRP2
Sulf- or Gluc-BAs
ASBT
T- or G-BAs
MRP3
OSTα
OSTβ
MRP4
Urinary output
Systemic Circulation


1 Secreted bile salts consist of 95% old, recycled bile salts and 5% newly synthesized bile salts.
Liver
3 Reabsorbed bile salts are recycled by enterohepatic circulation.
Bile salts
Cholesterol
Common bile duct
Gallbladder
Stomach
Sphincter of Oddi
Duodenum
Hepatic portal vein
Duct from pancreas
4 5% of bile salts are lost in feces.
Colon
Terminal ileum
2 95% of bile salts are reabsorbed by the small intestine.
KEY
= Enterohepatic circulation of bile salts



Fiorucci et al. J Lipid Research

Liver chemistry and function tests

Liver biochemistry

Test that indicate damage to hepatocytes

- **Aspartate aminotransferase (AST),** formerly called SGOT. The AST enzyme is also found in muscles and many other tissues besides the liver. **NV <40UI/L**
- **Alanine aminotransferase (ALT)**, formerly called SGPT. ALT is almost exclusively found in the liver. **NV < 40UI/L**

- AST/ALT >1000 UI/L occurs in extensive acute liver injury
- AST/ALT a ratio of 2-4 folds of normal occurs in chronic hepatitis
- AST:ALT ratio 2:1 is suggestive of alcoholic liver disease

Liver biochemistry
AST and ALT

Chronic, Mild Elevations, ALT > AST (<150 U/L or 5 × normal)

Hepatic Causes

α_1-Antitrypsin deficiency
Autoimmune hepatitis
Chronic viral hepatitis (B, C, and D)
Hemochromatosis
Medications and toxins
Steatosis and steatohepatitis
Wilson disease

Nonhepatic Causes

Celiac disease
Hyperthyroidism

Severe, Acute Elevations, ALT > AST (>1000 U/L or >20-25 × normal)

Hepatic Causes

Acute bile duct obstruction
Acute Budd-Chiari syndrome
Acute viral hepatitis
Autoimmune hepatitis
Drugs and toxins
Hepatic artery ligation
Ischemic hepatitis
Wilson disease

Severe, Acute Elevations, AST > ALT (>1000 U/L or >20-25 × normal)

Hepatic Cause

Medications or toxins in a patient with underlying alcoholic liver injury

Nonhepatic Cause

Acute rhabdomyolysis

Chronic, Mild Elevations, AST > ALT (<150 U/L, <5 × normal)

Hepatic Causes

Alcohol-related liver injury (AST/ALT > 2:1, AST nearly always <300 U/L)
Cirrhosis

Nonhepatic Causes

Hypothyroidism
Macro-AST
Myopathy
Strenuous exercise

*Virtually any liver disease can cause moderate aminotransferase elevations (5-15 × normal).

AST= SGOT
ALT=SGPT

Liver biochemistry

Tests that indicate a reduced liver mass (reduced biosynthetic activity)

- **Prothrombin time (PT):** A test of the time it takes for a blood sample to clot, under specific conditions in a lab. If low levels of clotting factors are present, the prothrombin time is longer. **NV 70-100%**
- **International normalized ratio** (INR): a standardized way for all labs to report PT, so their results can be compared accurately with each other. **>1.3**
- **Serum Albumin** levels are low in severe chronic liver diseases, because reduced protein synthesis. **NV >3.5 g/l**
- **Bilirubin**(see below)

Prothrombin time

Measures the activity of factor I (Fibrinogen), II (Prothrombin), V (Proaccelerin), VII (Proconvertin), and X (Stuart–Prower Factor)

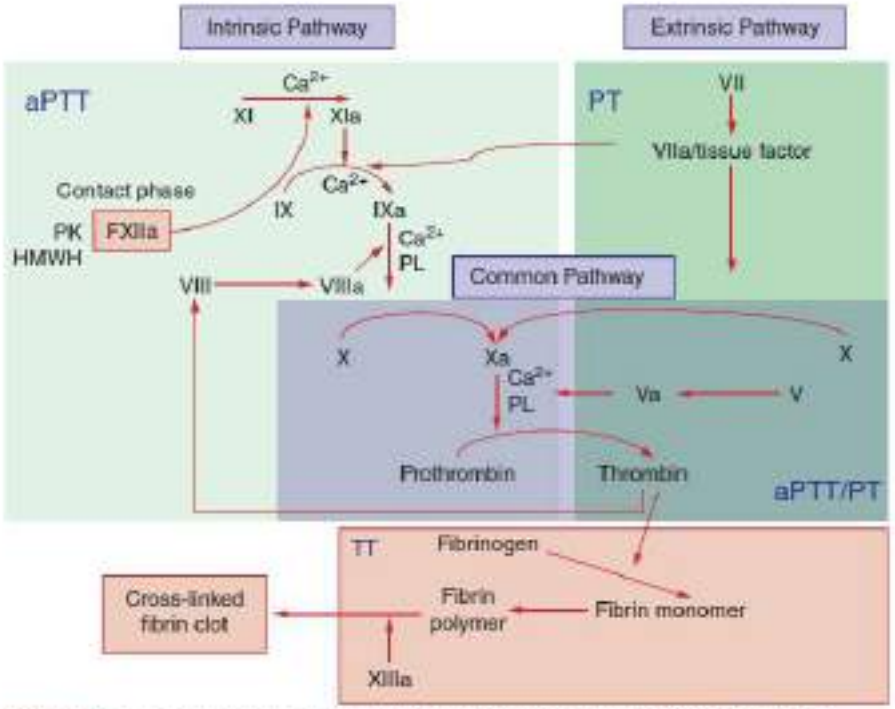


FIGURE 141-1 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).

Causes of Abnormal Prothrombin Time

- Deficiencies of Factor VII
- Deficiencies of Factor X
- Deficiencies of Factor V
- Deficiencies of Factor II
- Deficiencies of Fibrinogen
- Heparin
- Warfarin
- Fibrinogen/Fibrin Degradation Products
- Lupus Anticoagulant
- Liver Disease

Liver biochemistry

Test reflecting detoxification and excretion

Bilirubin

Indirect or unconjugated bilirubin

0.2-0.4 mg/dl

Direct bilirubin or conjugated

0.4-0.6 mg/dl

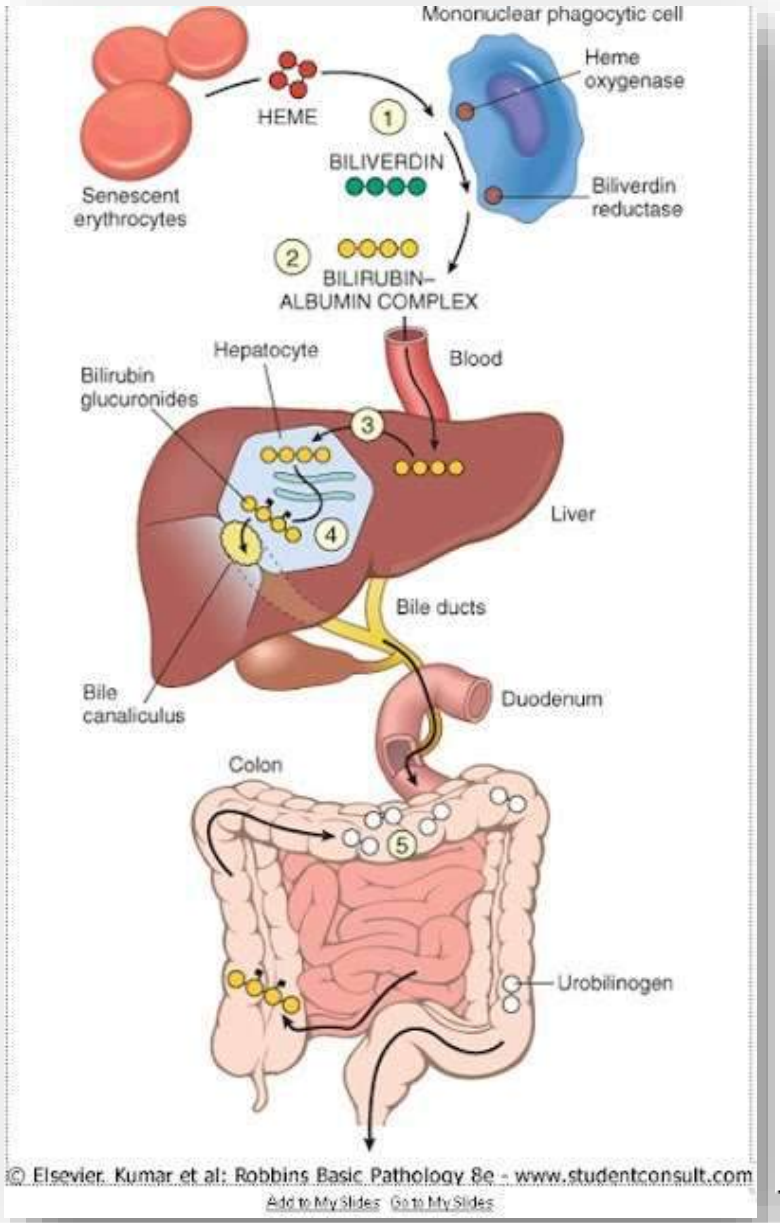
Total bilirubin

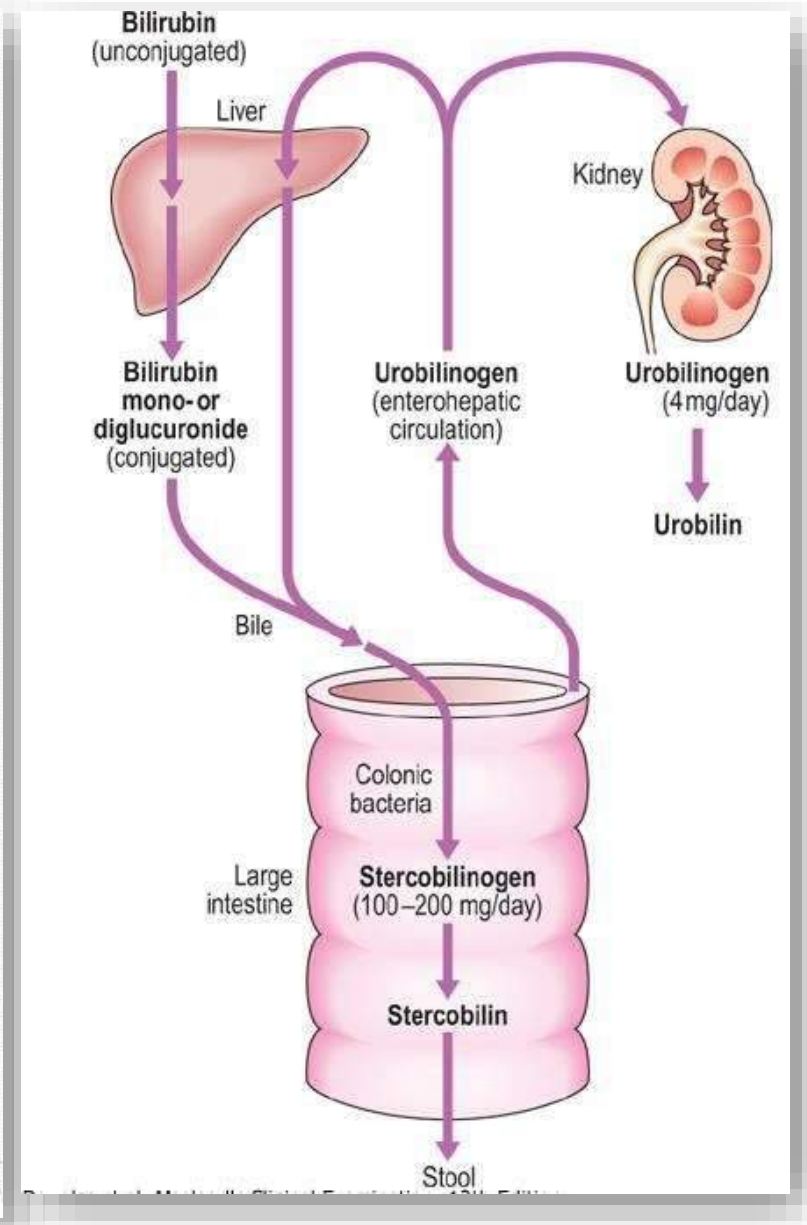
<1.2 mg/dl

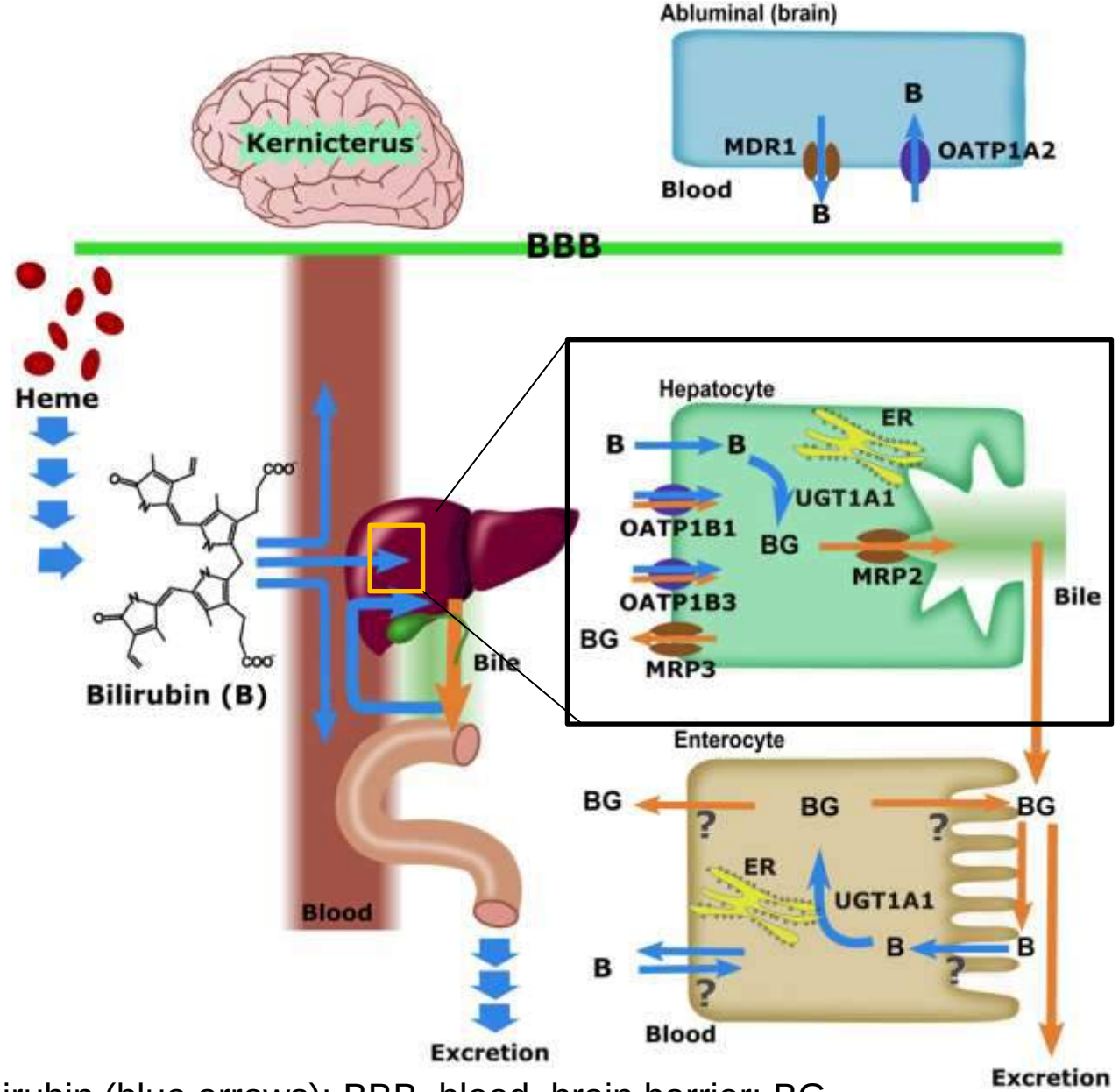
Jaundice may be noticeable in mucosas at levels of 2 to 3 mg/dL and in the skin at higher levels.

Urine urobilinogen (see below)

Bilirubin metabolism





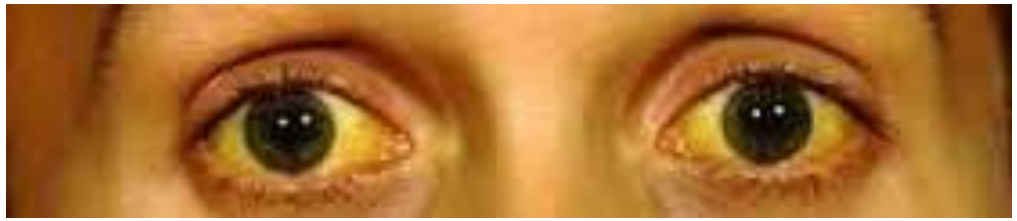


Abbreviations: B, bilirubin (blue arrows); BBB, blood–brain barrier; BG, bilirubin glucuronide (orange arrows); ER, endoplasmic reticulum; MDR, multidrug-resistance protein; MRP3, multidrug resistance-associated protein 3.

Hepatology, Volume: 67, Issue: 4, Pages: 1609-1619, First published: 23 October 2017, DOI: (10.1002/hep.29599)

Jaundice

Jaundice is a yellowish discoloration of the skin and other membranes including sclerae and mucus membrane caused by hyperbilirubinemia.



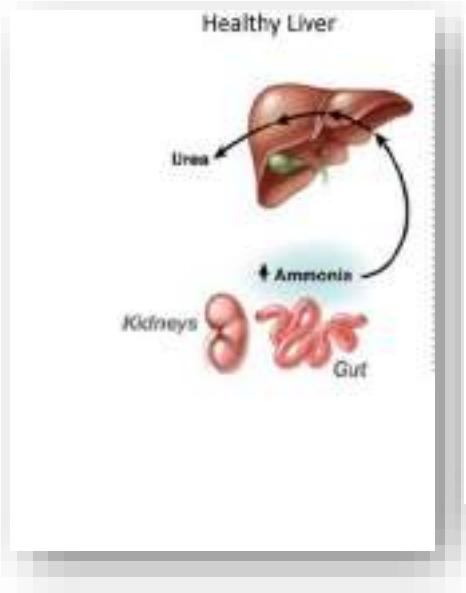
Hyperbilirubinamia is a sign of liver diseases or less frequently of a hemolytic disorder

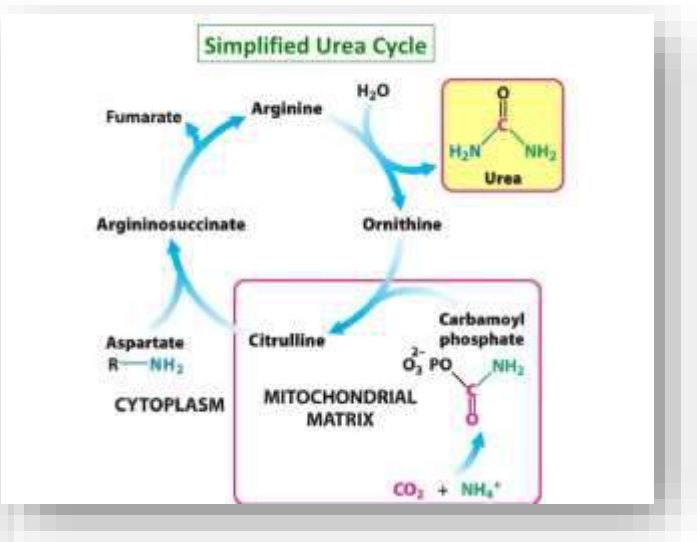
Harrison's Principles of internal medicine. 18 ed. 2012- Ch42

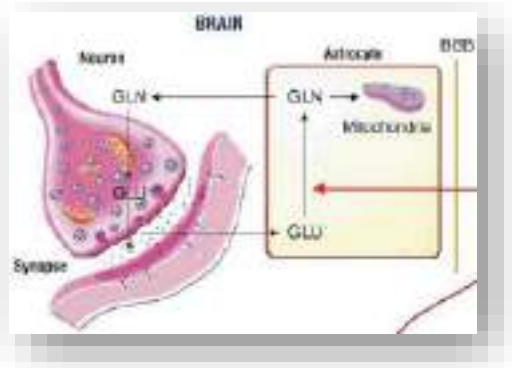
Liver biochemistry

Test reflecting detoxification and excretion

Ammonia is produced in the body during normal protein metabolism and by colon bacteria and recycled in the liver to generate urea.







Increased blood levels of ammonia associates to hepatic encelophathy

Liver biochemistry

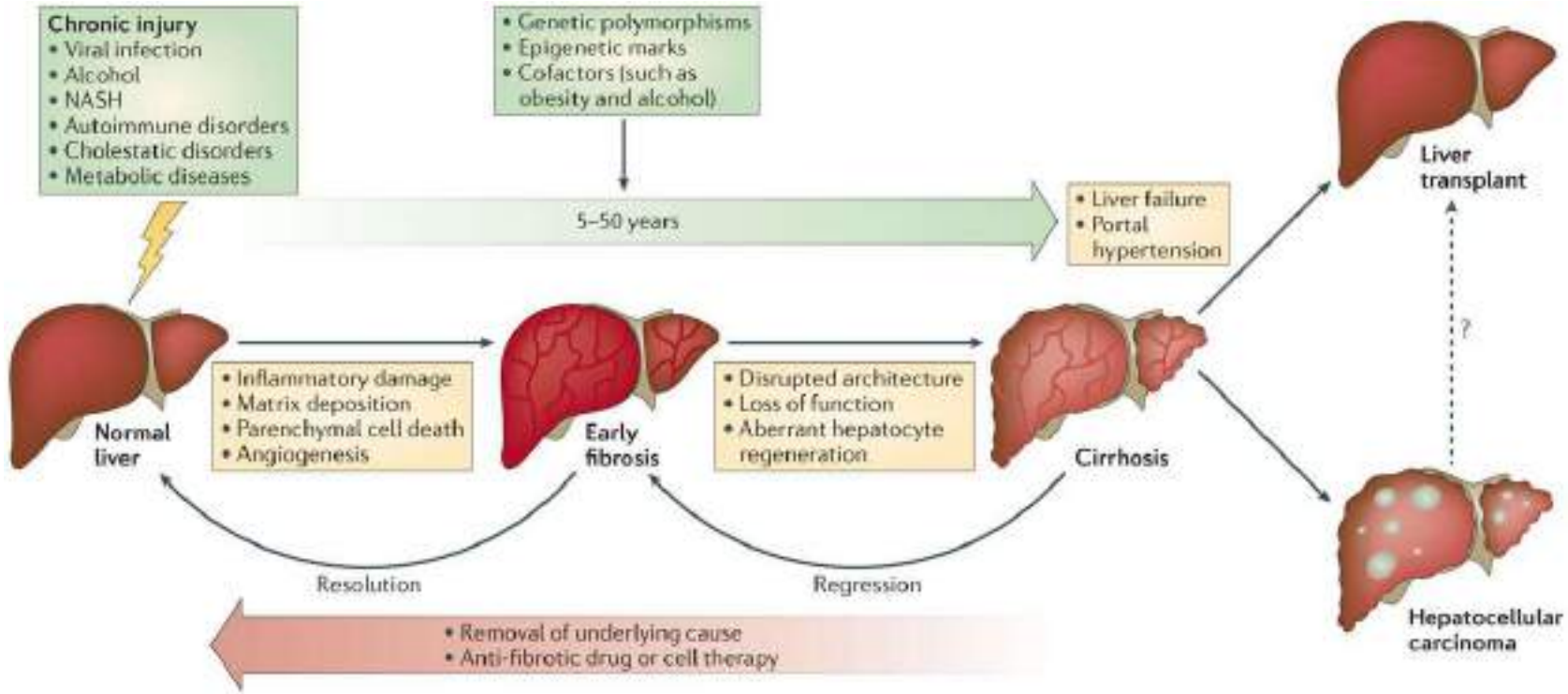
Enzymes that reflect biliary injury (cholestasis)

- **Alkaline phosphatase** **NV <120-180 UI/L**
- **Gamma-glutamyl transpeptidase** (γGT) **NV<50UI/L**
- **Bilirubin** (also indicates reduced detoxification ability)
- **Urine bilirubin (dark urine)** **urobilinogen 1-3 mg/dl**

Liver fibrosis

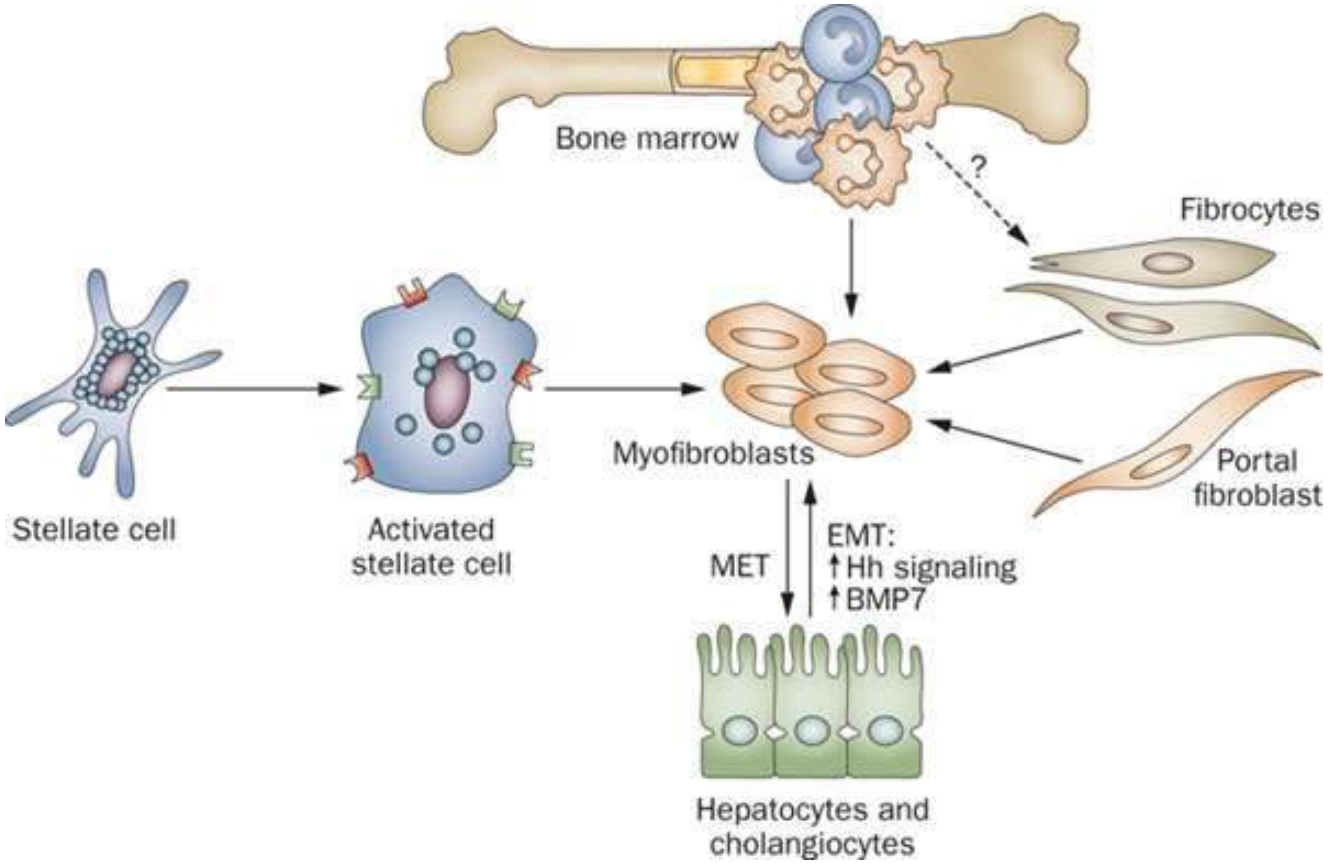
Liver fibrosis a pathological state that occurs in crhonic liver disorders and is associated with increased risk of progression toward liver cirrhosis.

Liver fibrosis is caused by activation of **hepatic stellate cells** (or Ito cells) and mesenchymal cells in repsonse to liver injury.



Nature Reviews | Immunology

Sources of fibrogenic cell types in hepatic fibrosis



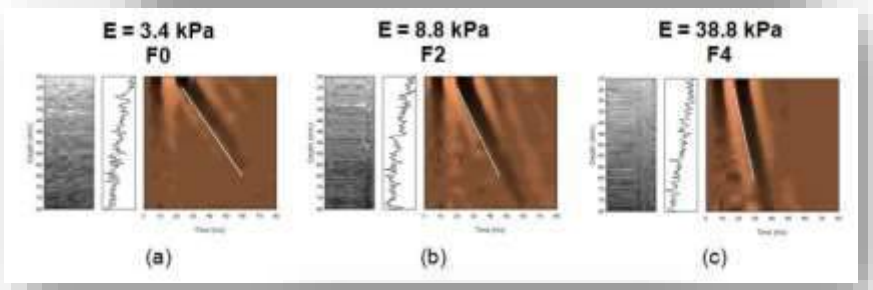
Friedman, S. L. (2010) Evolving challenges in hepatic fibrosis
Nat. Rev. Gastroenterol. Hepatol. doi:10.1038/nrgastro.2010.97

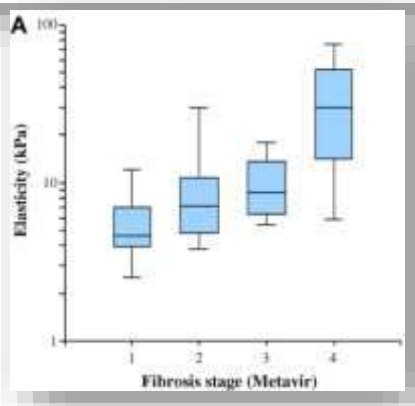
Liver fibrosis

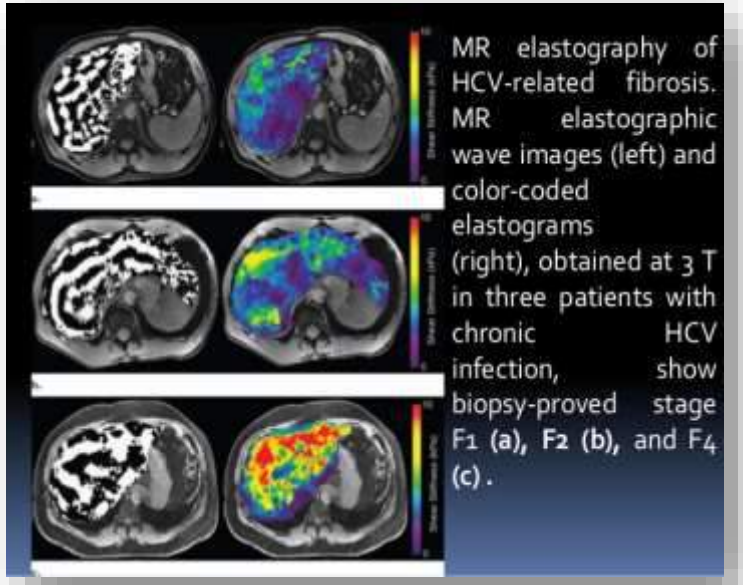
Assessment of liver fibrosis could be obtained by:

- **Biochemistry (APRI, FIB-4, etc)**
- **Transient elastography**
- **MR**
- **Liver biopsy**

Transient elastography







MR elastography of HCV-related fibrosis. MR elastographic wave images (left) and color-coded elastograms (right), obtained at 3 T in three patients with chronic HCV infection, show biopsy-proved stage F1 (a), F2 (b), and F4 (c).

Liver biochemistry

Enzymes that detect liver fibrosis

Fibro test or others

The test incorporate : Haptoglobin, bilirubin, γGT, apo-lipoprotein A1 and α2 -macroglobulin

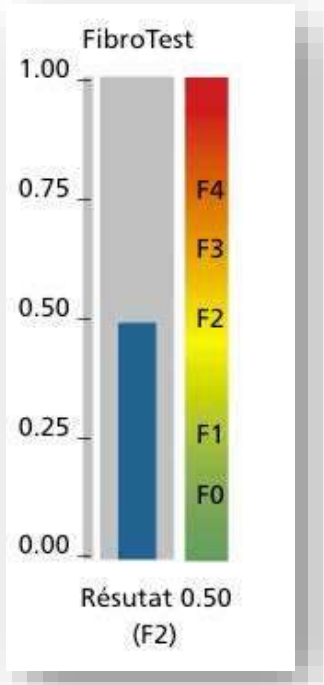


Table 1 "Indirect" serological markers for evaluation of liver fibrosis with relative sensitivity and specificity, as reported by the studies

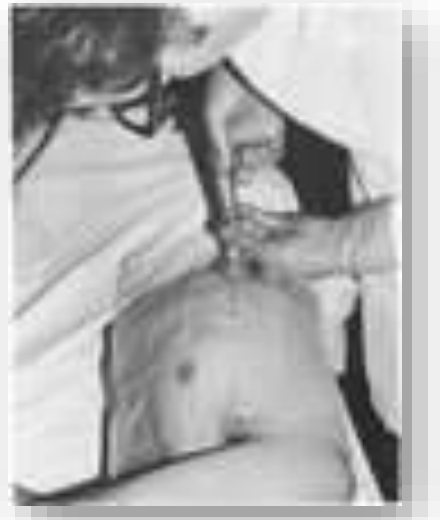
Name	Parameters	CLD	Sensitivity (%)	Specificity (%)	Study (ref)
PGA index	Prothrombin index, GGT, apolipoprotein A1	Mixed	91	81	2
PGAA index	Prothrombin index, GGT, apolipoprotein A1, α_2 macroglobulin	Alcohol	79	89	3
Bonacini index	Platelet count, ALT/AST ratio, INR	HCV	46	98	4
Fibrotest	α_2 macroglobulin, haptoglobin, γ-globulin, apolipoprotein A1, bilirubin	HCV	75	85	5
Forns fibrosis index	Age, platelet count, GGT, cholesterol	HCV	94	51	6
APRI index	AST/platelet ratio	HCV	89	75	7

Liver biopsy

LANDMARKS IN HEPATOLOGY

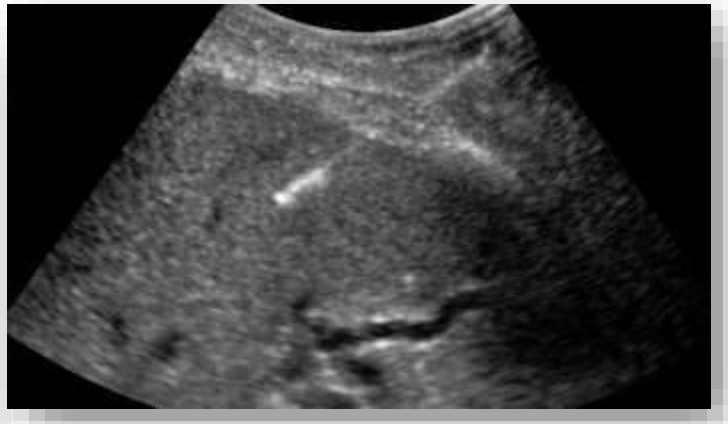
Just A Second

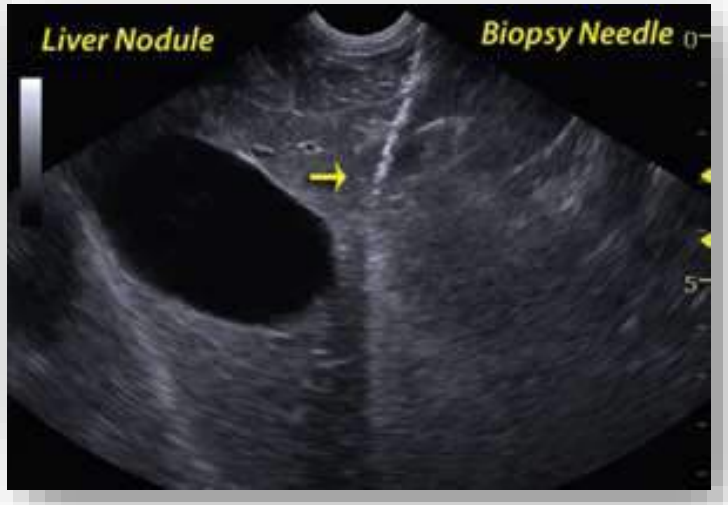
Fig. 1. Top: 7-cm × 1.6-mm Menghini needle c.1958, complete with skin-piercing stylet (above) and 3.5-cm "nail" shown partially inserted into the hub. A generous gift from Dr. Lee Sataline (Cheshire, CT). Middle: Diagrammatic representation of the successive steps of the Menghini technique of liver biopsy (reprinted with permission from the American College of Gastroenterology[33]). Bottom: Giorgio Menghini (2/14/1916-10/25/1983) in 1982. Photograph courtesy of Professore Stefano Fiorucci, provided by Menghini's daughter Chiara.

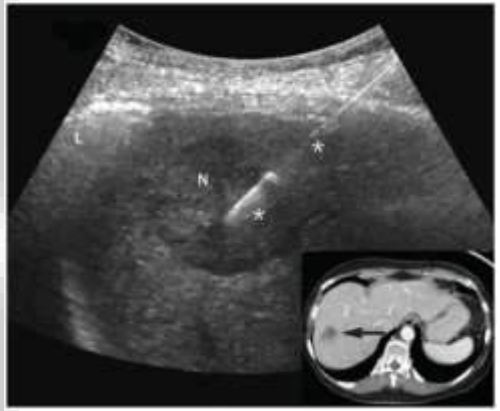


31. Menghini G. One-second needle biopsy of the liver. Gastroenterology 1958;35:190-199.
32. Menghini G. One-second biopsy of the liver—problems of its clinical application. N Engl J Med 1970;283:582-585.
33. Menghini G, Lauro G, Caracenti M. Some innovations in the technic of the one-second needle biopsy of the liver. Am J Gastroenterol 1975;64: 175-180.

Liver biopsy



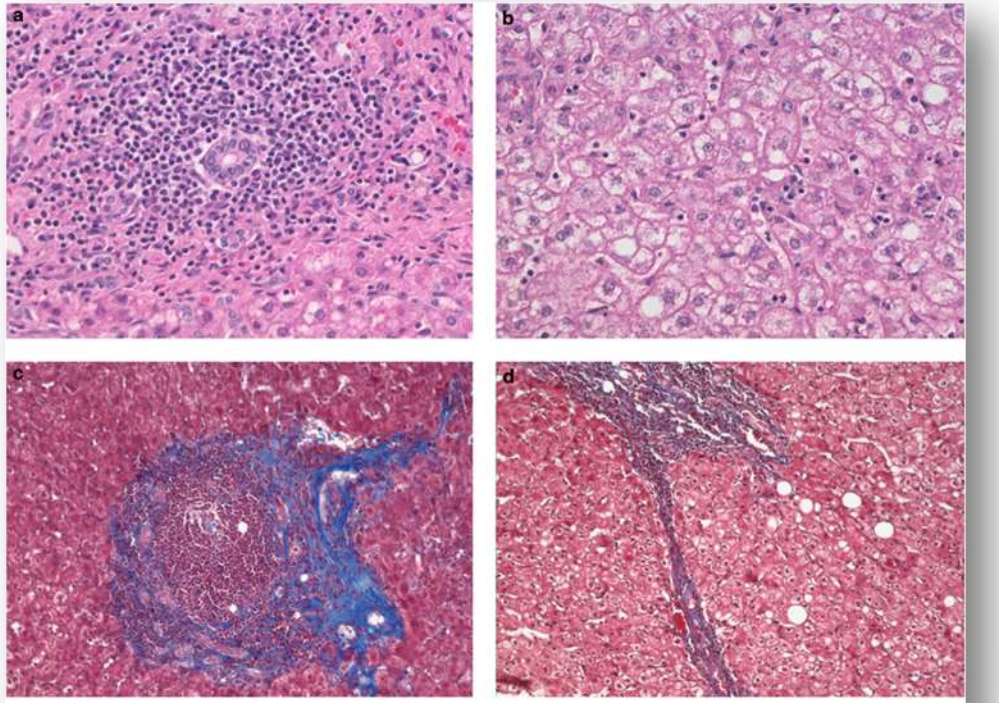


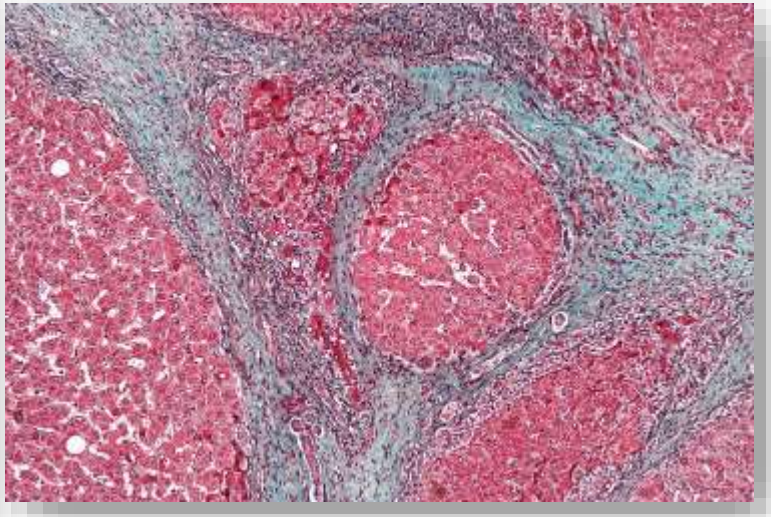


Liver Biopsy.mp4

EUS-FNA technique for subcapsular liver mets.avi.mp4

Liver histology





Chronic liver disorders can be discriminated by liver biopsy

Viral B and C

Autoimmune hepatitis

Genetic

Drugs-induced hepatitis

NASH

Alcohol

Liver disorders: staging

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged	<4	4-6	>6
or			
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

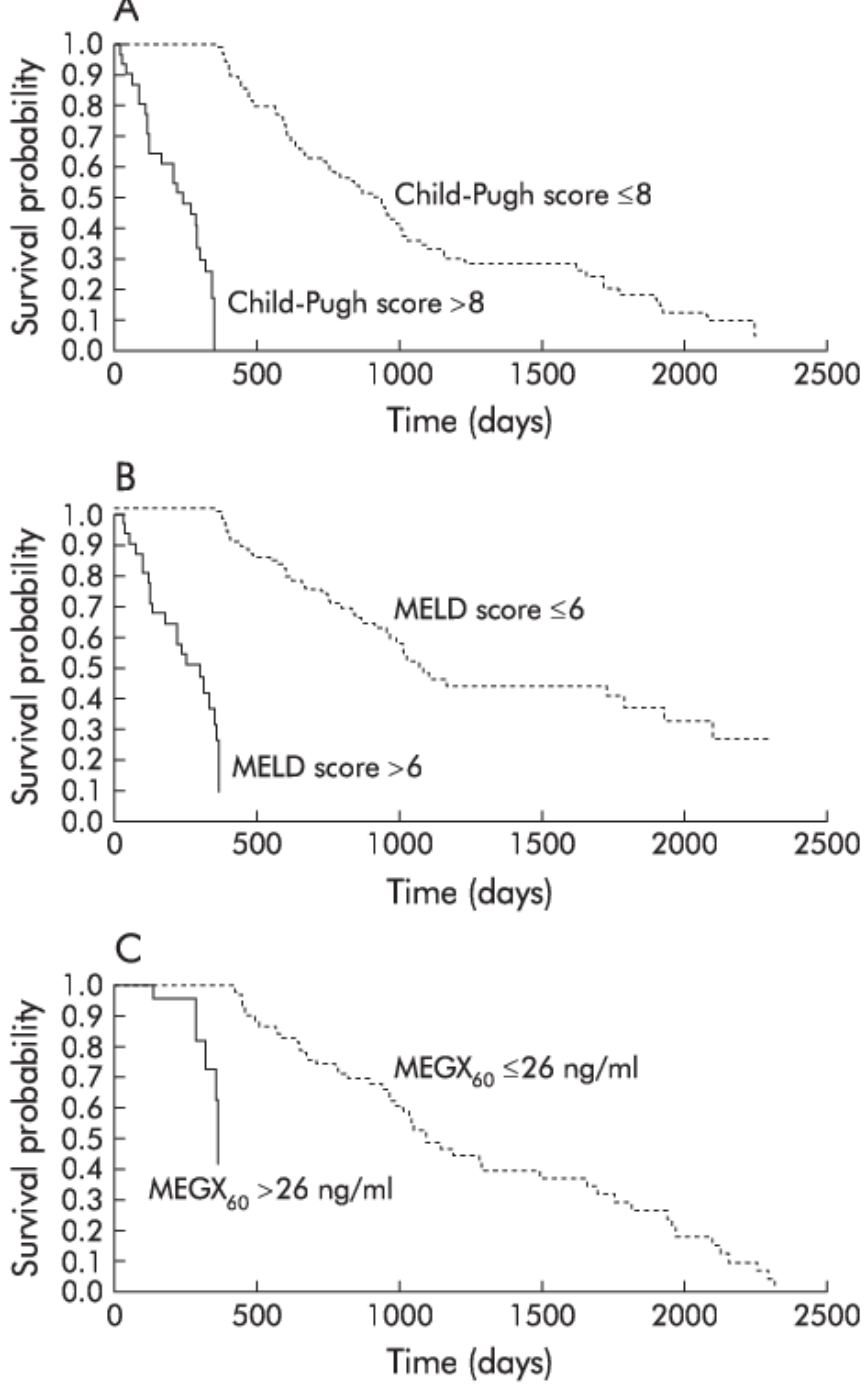
Liver disorders: staging

MELD = 3.78 x $\log_e$ serum bilirubin (mg/dL) +
11.20 x $\log_e$ INR +
9.57 x $\log_e$ serum creatinine (mg/dL) +
6.43 (constant for liver disease etiology)

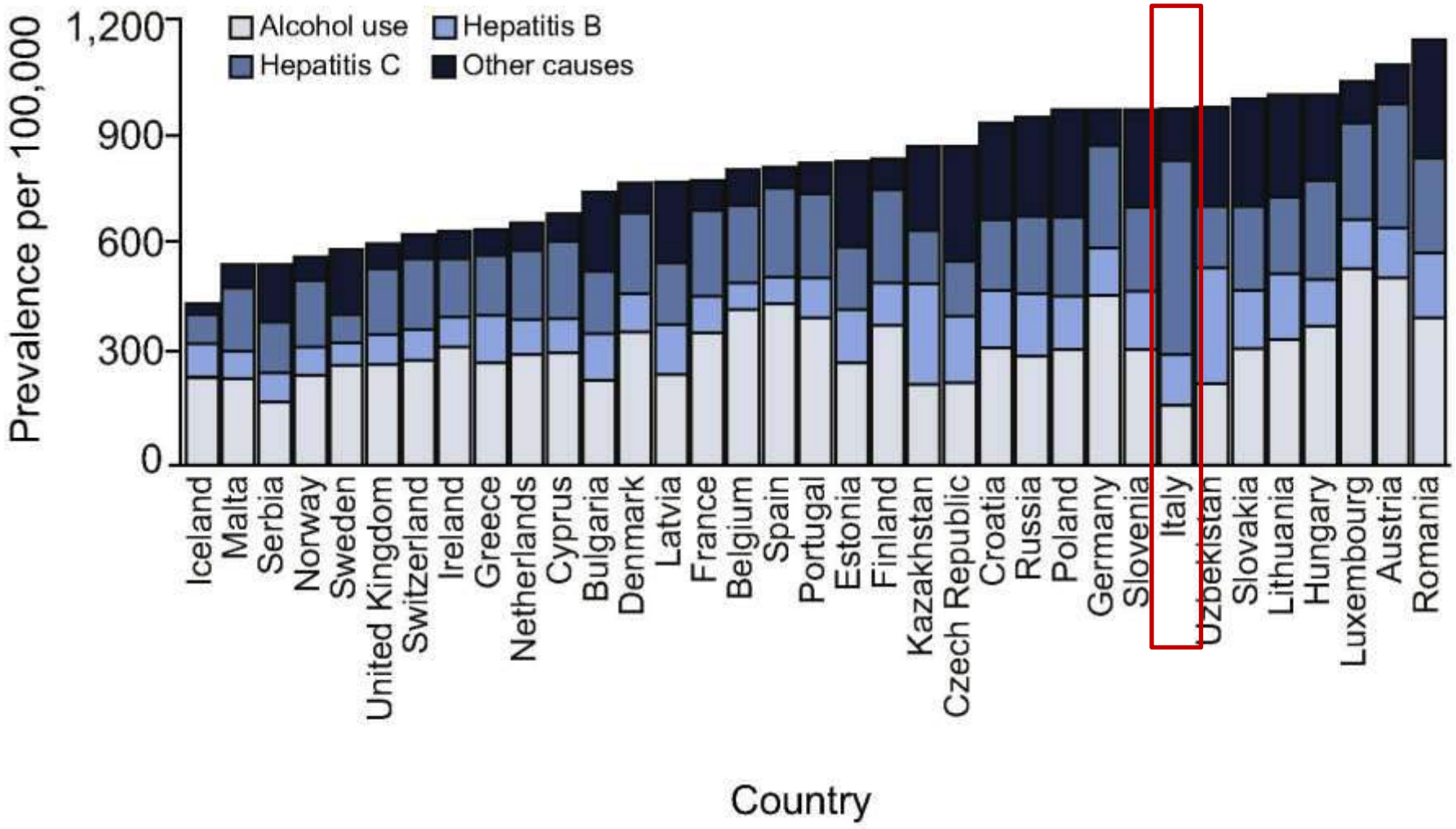
NOTES:

If the patient has been dialyzed twice within the last 7 days, then the value for serum creatinine used should be 4.0

Any value less than one is given a value of 1 (i.e. if bilirubin is 0.8, a value of 1.0 is used) to prevent the occurrence of scores below 0 (the natural logarithm of 1 is 0, and any value below 1 would yield a negative result)


A
Survival probability
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Child-Pugh score ≤8
Child-Pugh score >8
0
500
1000
1500
2000
2500
Time (days)
B
Survival probability
MELD score ≤6
MELD score >6
Time (days)
C
Survival probability
MEGX60 ≤26 ng/ml
MEGX60 >26 ng/ml
Time (days)

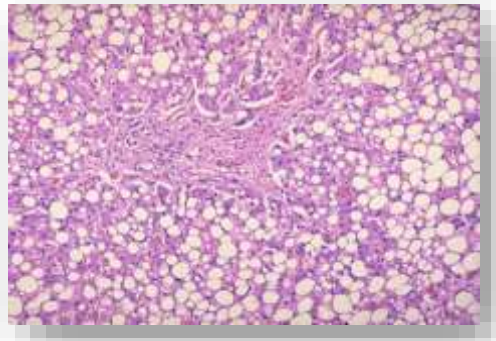
Liver diseases in Europe 2018



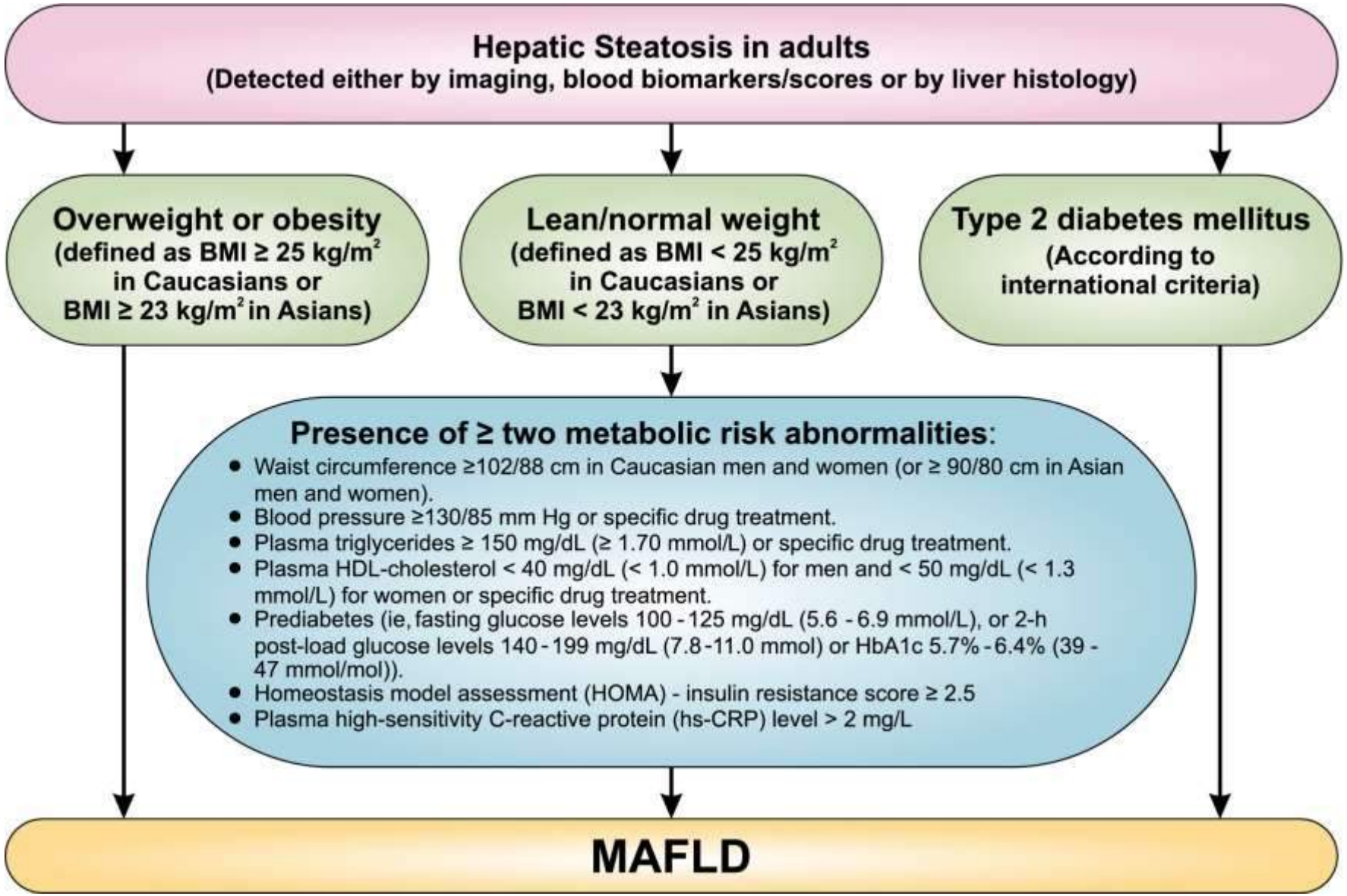
Source: Global Burden of Disease database

Fatty liver diseases: Changing Terminology

- **ALD:** Alcoholic Liver Disease
  Significant alcohol consumption*
  > 50 g/5-10 years for males
  > 25 gr/ 10 years for females
- **NAFLD**
- **MAFLD:** Non-Alcoholic Fatty Liver Disease
  steatosis without hepatocyte injury
- **NASH:** Non-Alcoholic Steatohepatitis
  steatosis with inflammation,
  hepatocyte injury with or without fibrosis



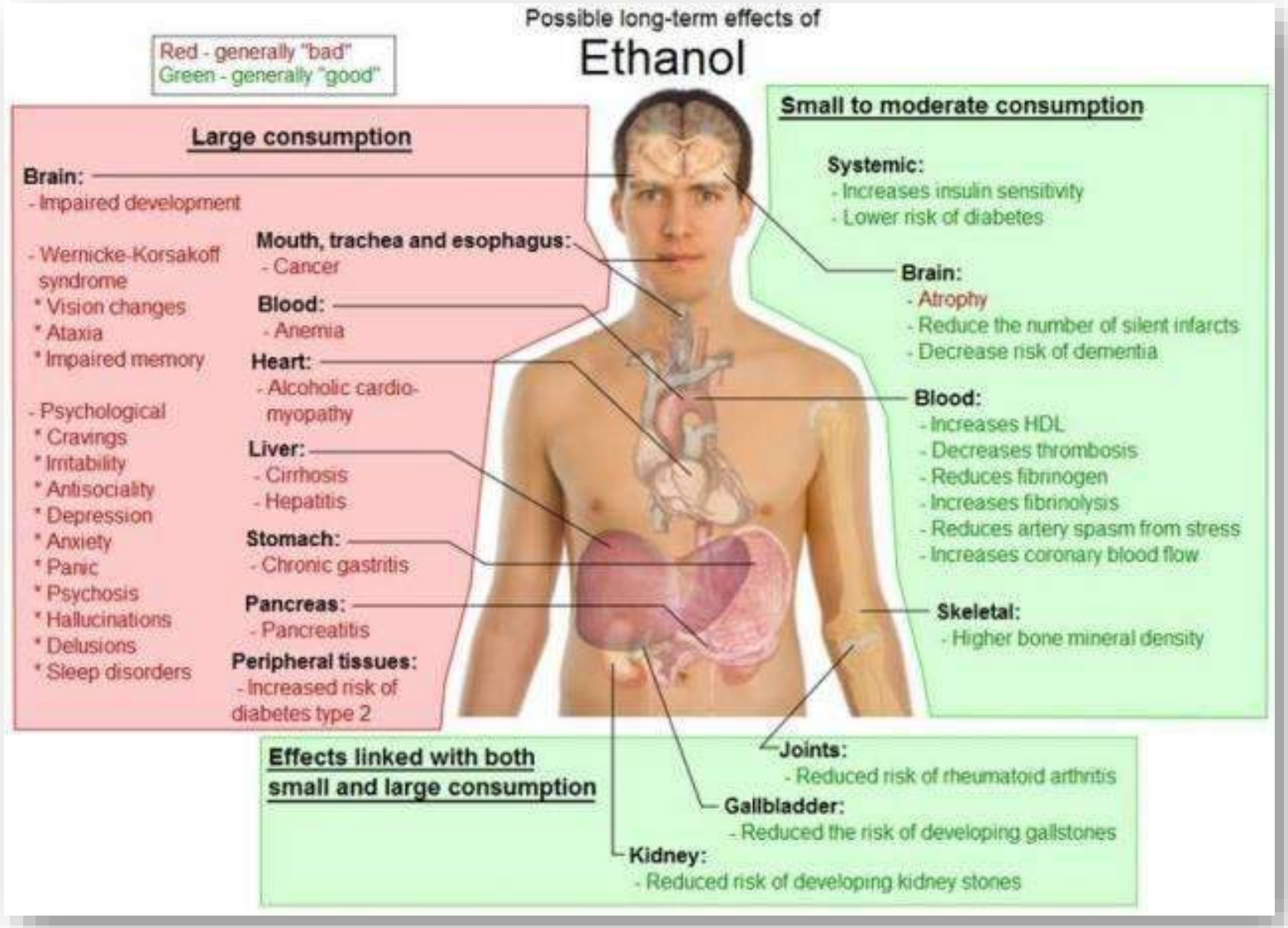
*Sanyal, et al *Hepatology* 2011



Liver International, Volume: 40, Issue: 6, Pages: 1254-1261, First published: 17 April 2020, DOI: (10.1111/liv.14478)

Alcoholic liver disease

Alcohol related diseases



Alcohol related diseases

Table 3 Alcohol-related discharges by disease type, 2005–2008 (N=13,710)

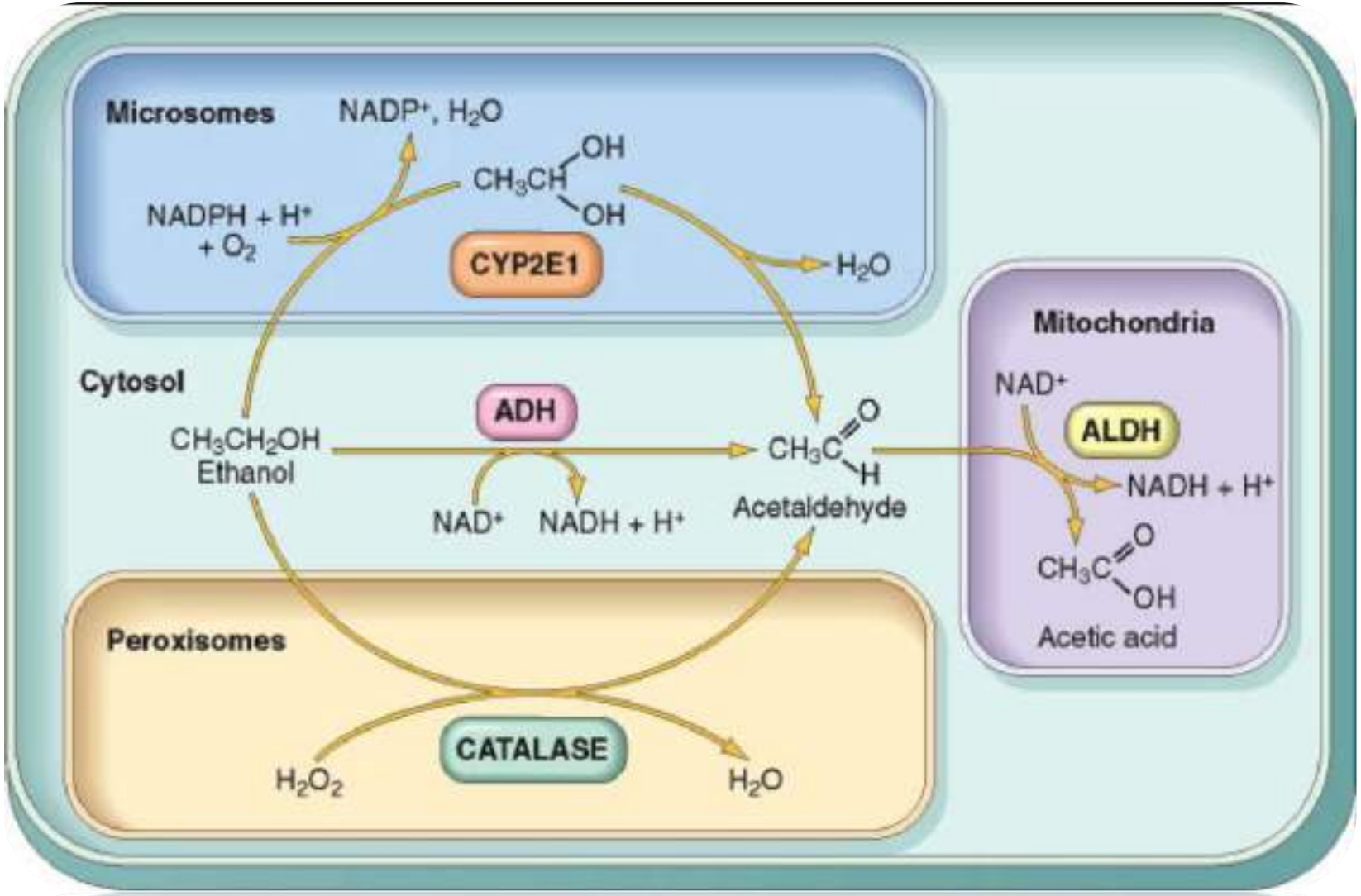
	Number	%
Alcoholic liver disease	10349	75.5
Alcoholic gastritis	1295	9.4
Alcohol-induced chronic pancreatitis	1198	8.7
Alcoholic cardiomyopathy	483	3.5
Degeneration of nervous system due to alcohol	272	2.0
Alcoholic myopathy	58	0.4
Alcoholic polyneuropathy	55	0.4

Alcoholic liver disease-pathogenesis

Alcohol is a direct hepatotoxin

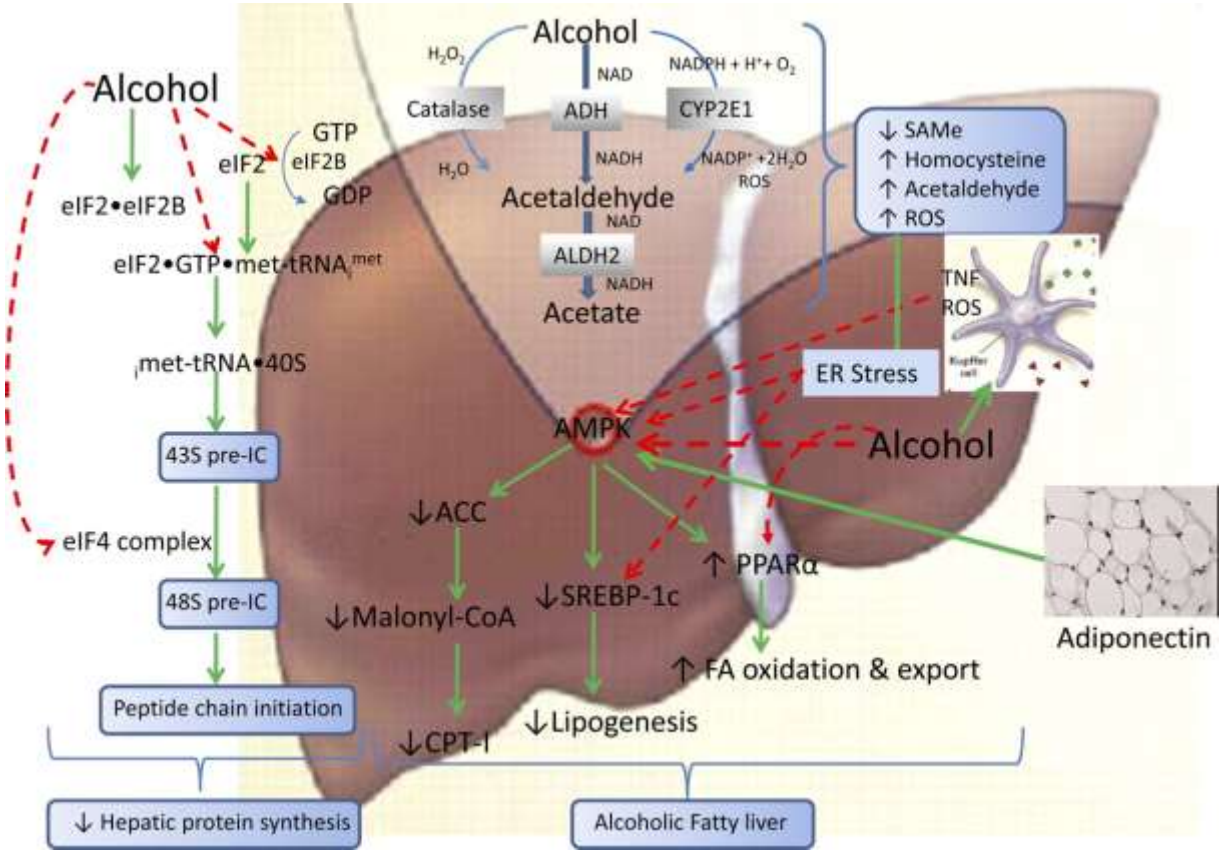
The hepatic metabolism of alcohol initiates a pathogenic process involving production of **toxic protein-aldehyde adducts**, **endotoxins, oxidative stress, immunologic activity, and pro-inflammatory cytokine release**.

Alcohol oxidation to acetaldehyde may occur through cytosolic alcohol dehydrogenase (ADH), cytochrome P-450 (CYP)2E1, or peroxisomal catalase (in that order of importance).



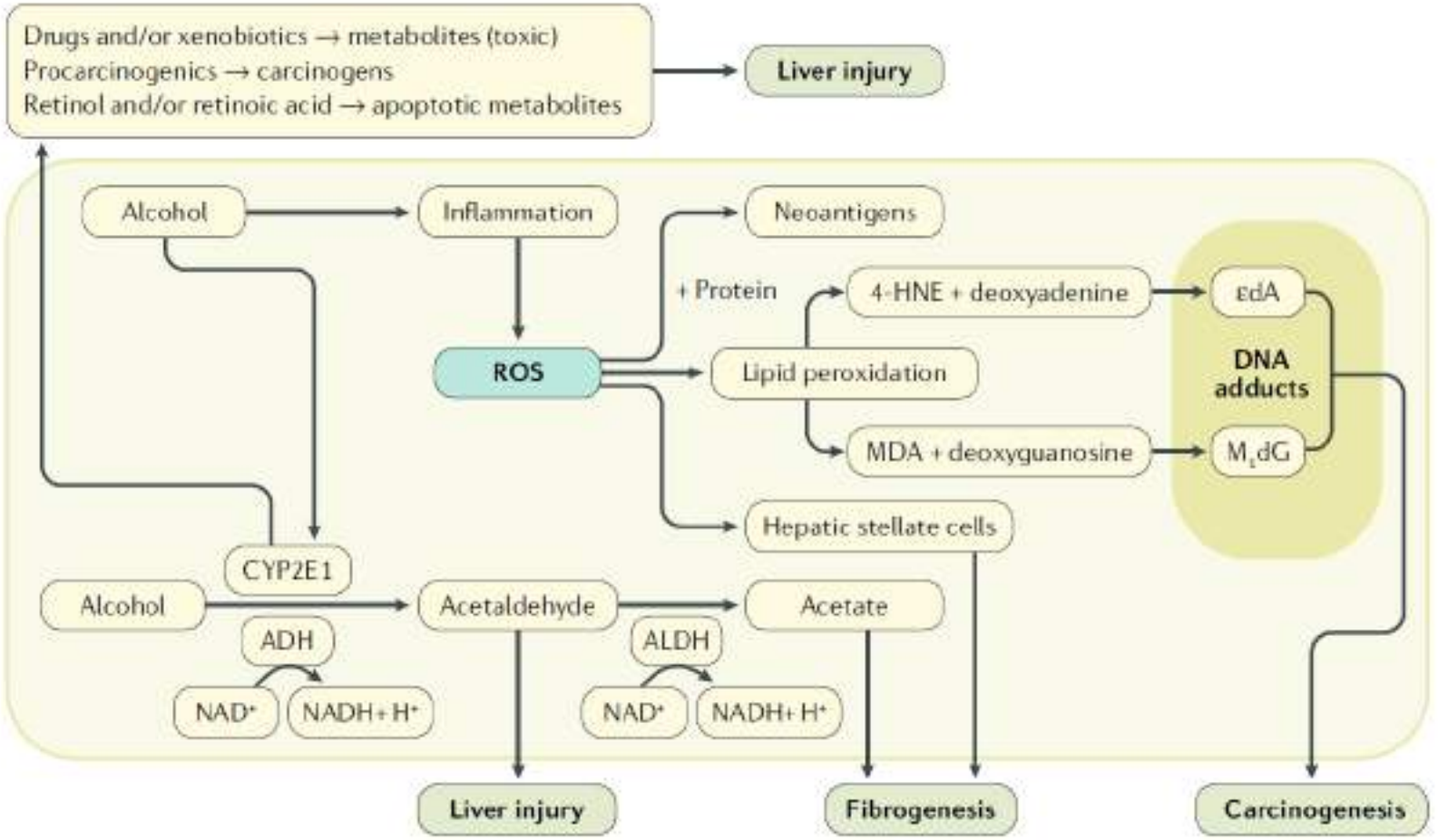
Alcohol oxidation to acetaldehyde may occur through cytosolic alcohol dehydrogenase (ADH), cytochrome P-450 2E1, or peroxisomal catalase (in that order of importance).

AMP kinase (AMPK), a key regulator of metabolism, drives fatty acid (FA) oxidation and export through activation of peroxisome proliferator-activated receptor-α (PPARα); suppresses SREBP-1c, decreasing lipogenesis; and inhibits acetyl-CoA carboxylase (ACC), which through decreased malonyl-CoA levels and carnitine palmitoyltransferase I (CPT I) activity decreases synthesis and increases oxidation of fatty acids.



Patricia E. Molina Am J Physiol Endocrinol Metab 2008;295:E1-E2

Alcoholic liver disease: oxidative damage



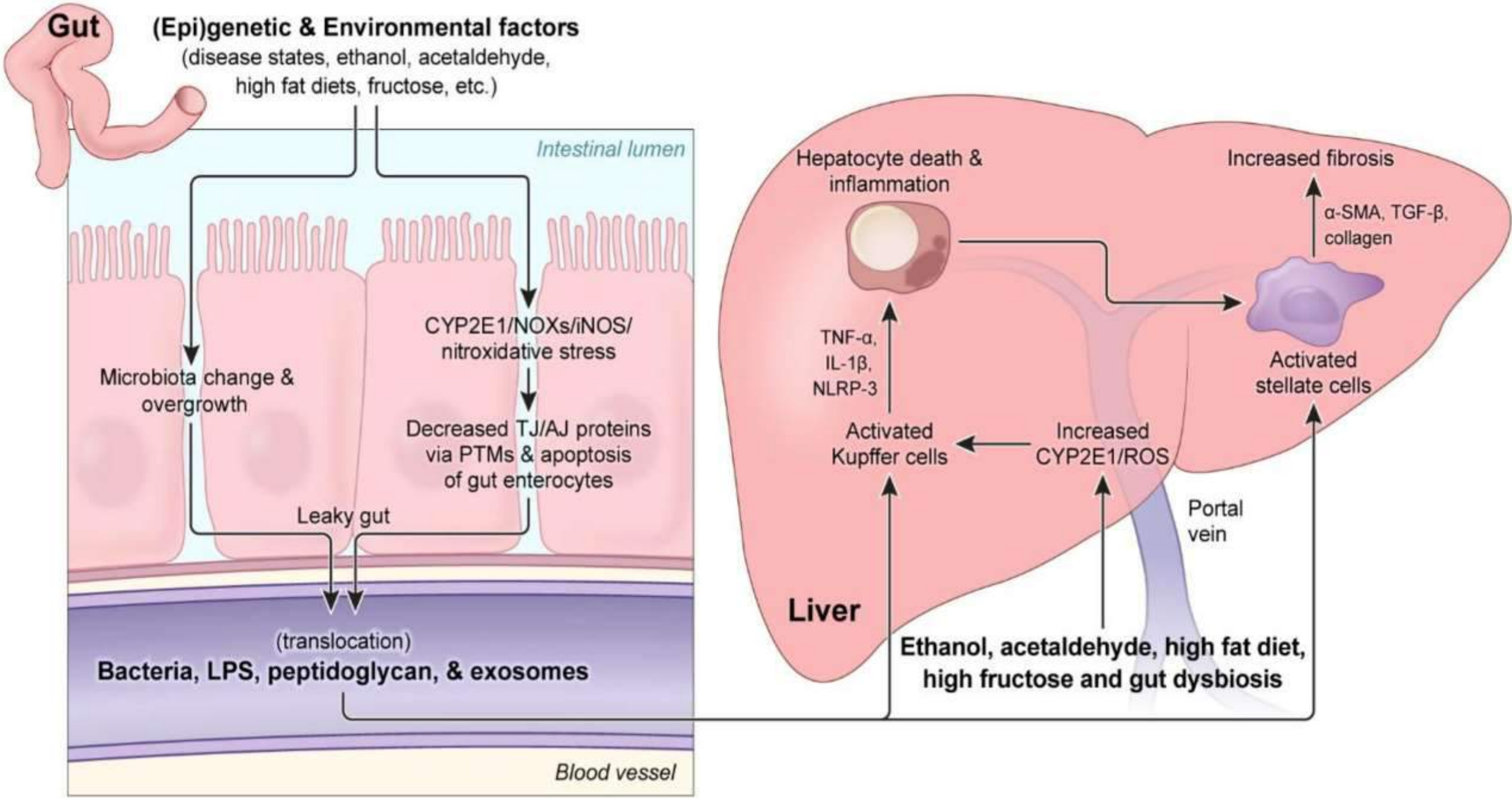

Gut
(Epi)genetic & Environmental factors
(disease states, ethanol, acetaldehyde,
high fat diets, fructose, etc.)
Intestinal lumen
Microbiota change &
overgrowth
CYP2E1/NOXs/iNOS/
nitroxidative stress
Decreased TJ/AJ proteins
via PTMs & apoptosis
of gut enterocytes
Leaky gut
(translocation)
Bacteria, LPS, peptidoglycan, & exosomes
Blood vessel
Hepatocyte death &
inflammation
Increased fibrosis
α-SMA, TGF-β,
collagen
TNF-α,
IL-1β,
NLRP-3
Activated
stellate cells
Activated
Kupffer cells
Increased
CYP2E1/ROS
Portal
vein
Liver
Ethanol, acetaldehyde, high fat diet,
high fructose and gut dysbiosis

TABLE 467-1 EFFECTS OF BLOOD ALCOHOL LEVELS IN THE ABSENCE OF TOLERANCE

Blood Level, g/dL	Usual Effect
0.2 g/L	Decreased inhibitions, a slight feeling of intoxication
0.8 g/L	Decrease in complex cognitive functions and motor performance
2 g/L	Obvious slurred speech, motor incoordination, irritability, and poor judgment
3 g/L	Light coma and depressed vital signs
4 g/L	Death

Da 0,5 g/l a 0,8 g/l
ammenda da 500€ a 2.000€;
sospensione patente da 3 a 6 mesi;
Da 0,8 g/l a 1,5 g/l
ammenda da 800€ a 3.200€;
arresto fino a 6 mesi;
sospensione patente da 6 mesi a un anno;
Superiore a 1,5 g/l
ammenda da 1.500€ a 6.000€;
arresto da 6 mesi ad 1 anno;
sospensione patente da 1 a 2 anni;
sequestro preventivo del veicolo;
confisca del veicolo (ciò non avviene se il mezzo appartiene ad una persona estranea al reato).

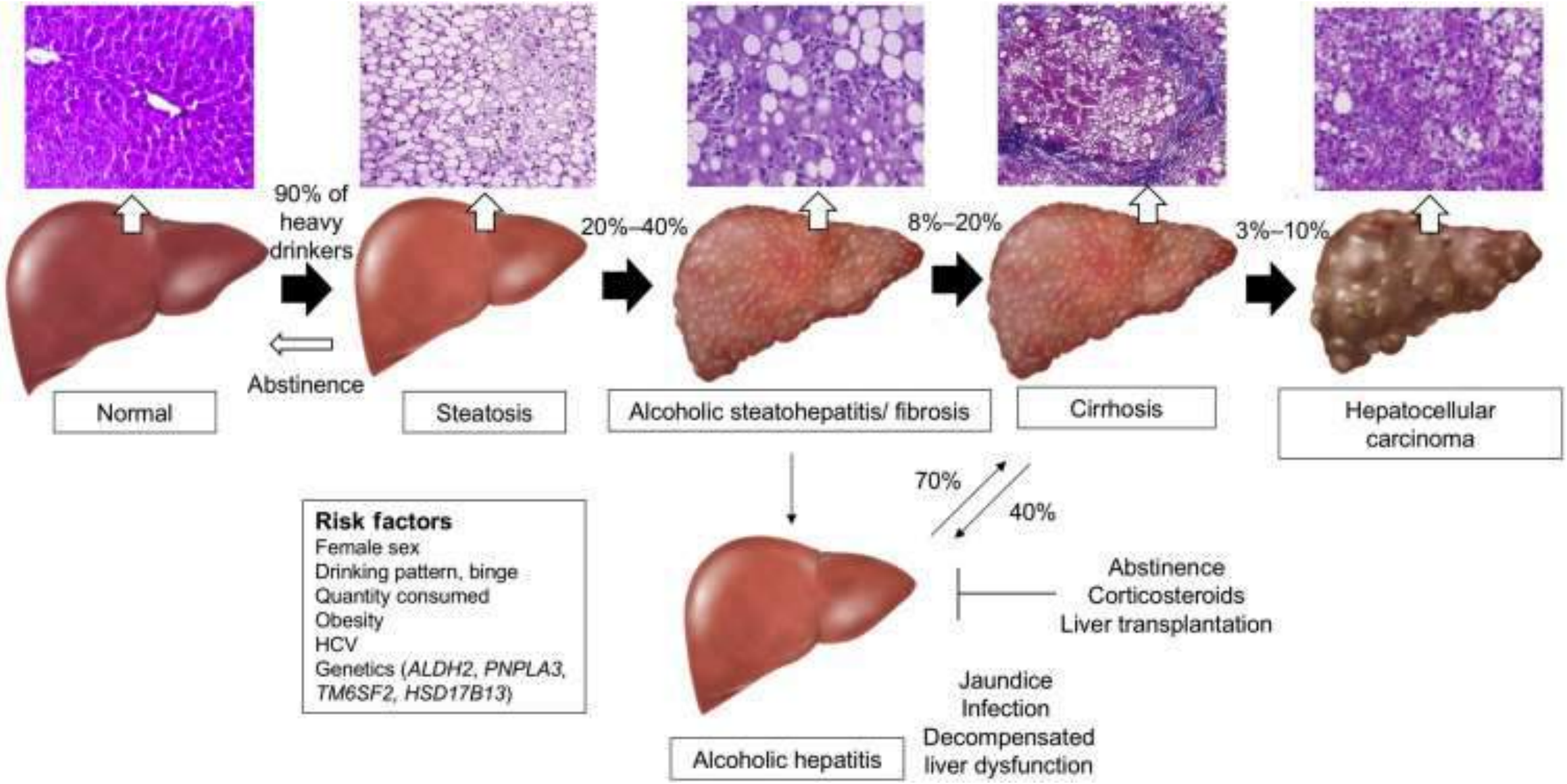
Alcoholic liver disease (ALD)

Chronic and excessive alcohol ingestion is one of the major causes of liver disease.

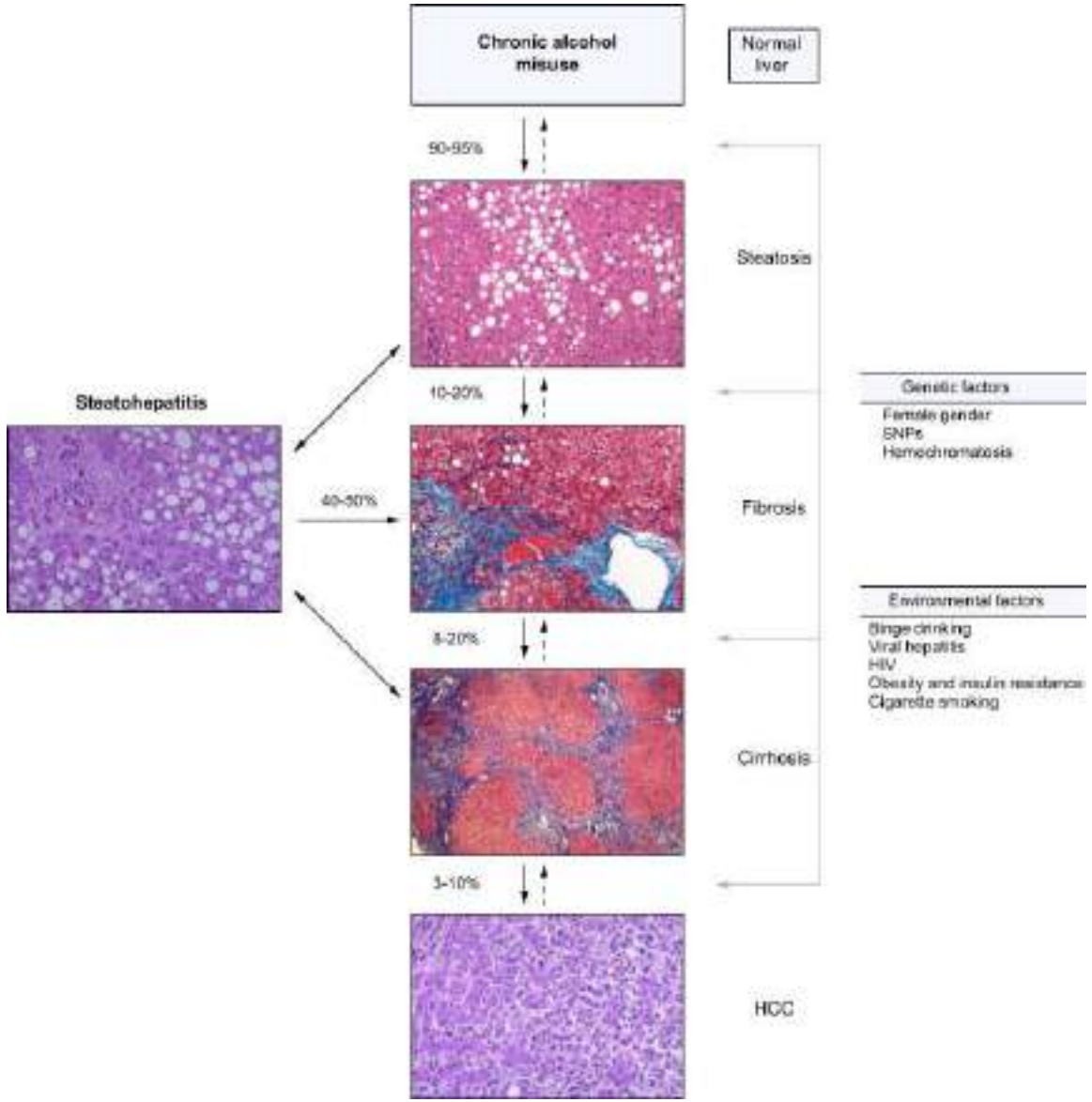
The pathology of alcoholic liver disease comprises two major lesions, with the injury rarely existing in a pure form:

(1)fatty liver (steatosis and steatohepatitis)

(2) cirrhosis.


90% of heavy drinkers
Abstinence
20%–40%
8%–20%
3%–10%
Normal
Steatosis
Alcoholic steatohepatitis/ fibrosis
Cirrhosis
Hepatocellular carcinoma
Risk factors
Female sex
Drinking pattern, binge
Quantity consumed
Obesity
HCV
Genetics (ALDH2, PNPLA3, TM6SF2, HSD17B13)
70%
40%
Abstinence
Corticosteroids
Liver transplantation
Jaundice
Infection
Decompensated liver dysfunction
Alcoholic hepatitis

Alcoholic liver disease (ALD)



Alcoholic liver disease – natural history

Fatty liver is present in >90% of binge and chronic drinkers.

A much smaller percentage of heavy drinkers will progress to **alcoholic hepatitis**, or **cirrhosis.**

The prognosis of severe alcoholic liver disease is dismal;

the mortality of patients with alcoholic hepatitis concurrent with cirrhosis is nearly 60% at 4 years.

Although alcohol is considered a **direct hepatotoxin**, only between 10 and 20% of alcoholics will develop alcoholic hepatitis (comorbid factors such as gender, heredity and immunity)

Alcoholic liver disease – natural history

Risk threshold of alcohol consumption for liver cirrhosis

An important aspect of public health policy concerning alcohol has been the attempt to establish a safe threshold for consumption.

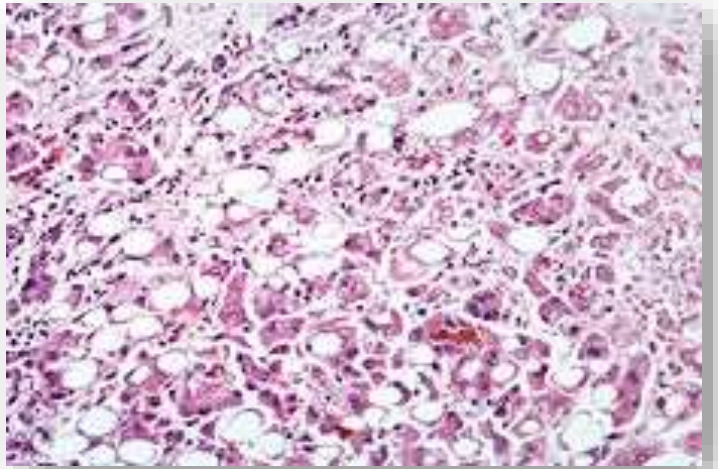
This revolves primarily around the extent to which moderate alcohol consumption is cardioprotective.

This positive effect of alcohol, if real, can then offset the large array of negative health consequences of even moderate alcohol consumption.

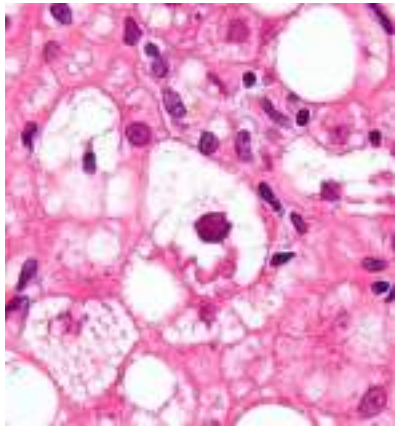
In a meta-analysis of daily consumption levels in relation to cirrhosis, patients taking **50 g of ethanol a day per 5-10 years increases the risk to develop cirrhosis.**

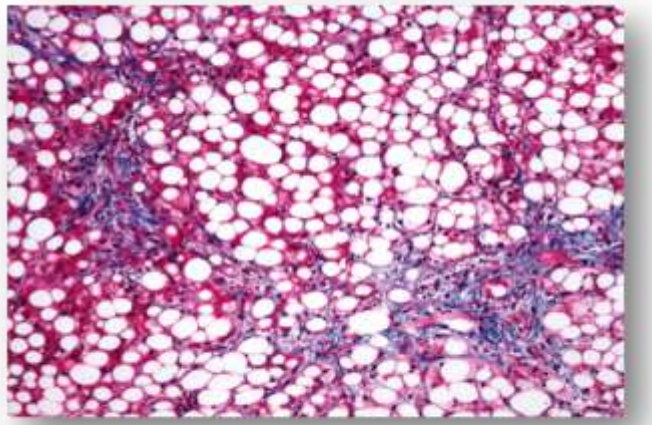
Alcoholic liver disease- histopathology

- **Fatty liver is the initial and most common histologic response to hepatotoxic stimuli, including excessive alcohol ingestion**. The accumulation of fat within the perivenular hepatocytes coincides with the location of **alcohol dehydrogenase**, the major enzyme responsible for alcohol metabolism.
- Continuing alcohol ingestion results in fat accumulation throughout the entire hepatic lobule.
- **Despite extensive fatty change and distortion of the hepatocytes with macrovesicular fat, the cessation of drinking results in normalization of hepatic architecture and fat content within the liver.**



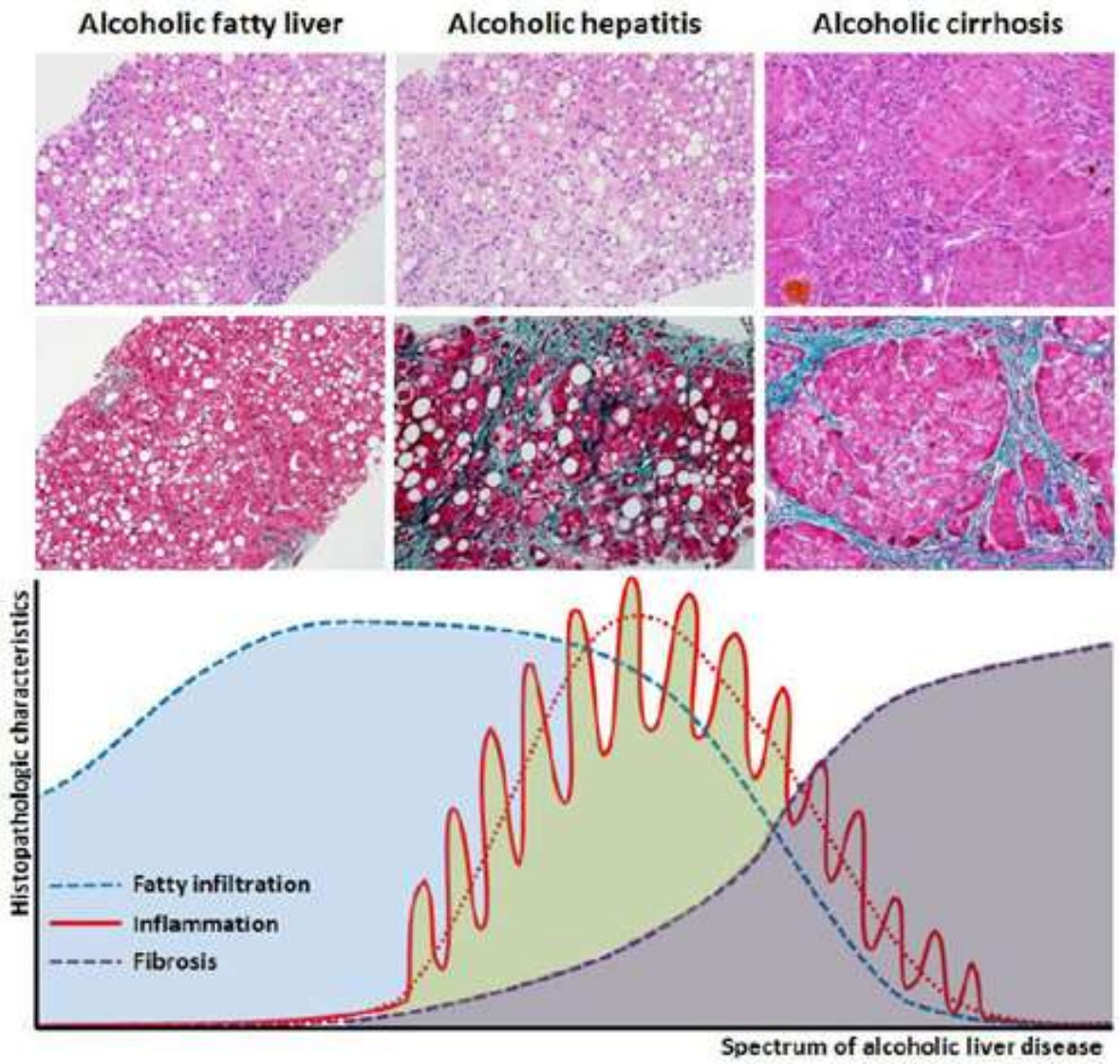
Alcoholic liver disease- histopathology





- Alcoholic fatty liver has traditionally been regarded as entirely benign, but similar to the spectrum of nonalcoholic fatty liver disease the appearance of **steatohepatitis and certain pathologic features such as giant mitochondria, perivenular fibrosis, and macrovesicular fat may be associated with progressive liver injury.**
- Mallory bodies are often present in florid cases but are neither specific nor necessary to establishing the diagnosis. Alcoholic hepatitis is thought to be a precursor to the development of cirrhosis. However, like fatty liver, it is potentially reversible with cessation of drinking. Cirrhosis is present in up to 50% of patients with biopsy-proven alcoholic hepatitis and its regression is uncertain, even with abstention

Alcoholic liver disease-histopathology progression



Alcoholic liver disease

Clinical presentation

Alcoholic liver disease

- The clinical manifestations of alcoholic fatty liver are subtle and characteristically detected as a consequence of the patient's visit for a seemingly unrelated matter.
- Previously unsuspected hepatomegaly is often the only clinical finding. Occasionally, patients with fatty liver will present with right upper quadrant discomfort, tender hepatomegaly, nausea, and jaundice.
- **Differentiation of alcoholic fatty liver from nonalcoholic fatty liver is difficult unless an accurate drinking history is ascertained.**

Alcoholic liver disease

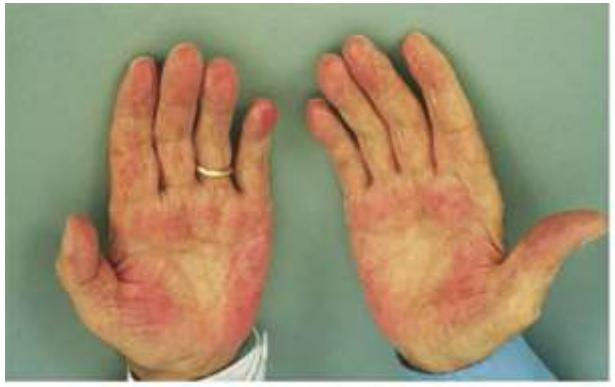
Most patients with moderate forms of ALD are asymptomatic and it can only be detected by appropriate screening methods.

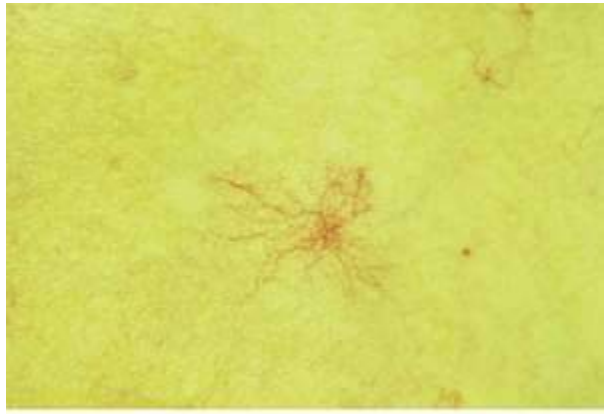
Some patients can show signs suggestive of harmful alcohol drinking such **as bilateral parotid gland hypertrophy**, **muscle wasting, malnutrition, Dupuytren's sign, and signs of symmetric peripheral neuropathy**.

In patients with cirrhosis, most physical findings are not specific of the etiology. However, some signs **such gynecomastia and extensive spider angiomas** may be more frequently seen in those with alcohol as the main cause of liver disease.

Alcoholic liver diseases

- On physical examination, the liver and spleen may be enlarged, with the liver edge being firm and nodular.
- Other frequent findings include scleral icterus, palmar erythema & spider angiomas parotid gland enlargement, digital clubbing, muscle wasting, or the development of edema and ascites.
- Men may have decreased body hair and gynecomastia
- Testicular atrophy, which may be a consequence of hormonal abnormalities or a direct toxic effect of alcohol on the testes.
- In women with advanced alcoholic cirrhosis, menstrual irregularities usually occur, and some women may be amenorrheic. These changes are often reversible following cessation of alcohol





Alcoholic liver disease

Laboratory Features

- Patients with alcoholic liver disease are often identified through routine screening tests. The typical laboratory abnormalities seen in fatty liver are nonspecific and include:

1. **modest elevations of the aspartate aminotransferase (AST), alanine aminotransferase (ALT),**
2. **glutamyl transpeptidase (γGT),**
3. **Increased MCV**
4. **aaccompanied by hypertriglyceridemia, hypercholesterolemia, and occasionally hyperbilirubinemia.**

- In alcoholic hepatitis and in contrast to other causes of fatty liver, the AST and ALT are usually elevated two- to sevenfold. They are rarely >400 IU, and the AST/ALT ratio >1

Diagnostic tests in the management of ALD: **Indirect markers** of alcohol consumption

Biomarker	Biological material	Detection window	EtOH amount	Sens.	Spec.	Confounding factors
GGT	Serum		Chronic excessive	42–86%	40–84%	Liver disease, BMI, sex, drugs
AST	Serum		Chronic excessive	43–68%	56–95%	Liver and muscle diseases, BMI, drugs
ALT	Serum		Chronic excessive	30–50%	51–92%	Liver disease, BMI, drugs
MCV	Serum		Chronic excessive	24–75%	56–96%	Vitamin B12, folic acid deficiency, haematological diseases
% CDT	Serum	1–2 weeks	50–80 g/d for >1–2 weeks	25–84%	70–98%	Liver cirrhosis/disease, nicotine, transferrin level, weight, sex, pregnancy, rare genetic variations

Diagnostic performance of indirect markers is not adequate

EASL CPG ALD. J Hepatol 2018;69:154–81

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Carbohydrate-deficient transferrin (**CDT**)

Diagnostic tests in the management of ALD: **Direct markers** of alcohol consumption

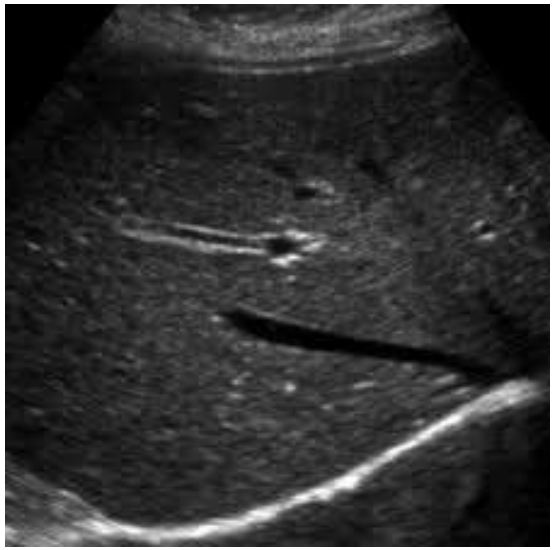
- Direct markers have higher specificity than indirect markers

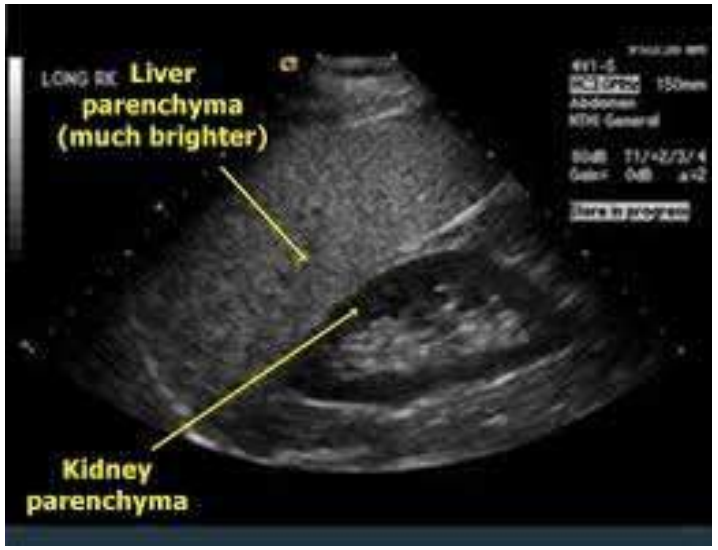
Biomarker	Biological material	Detection window	EtOH amount	Sens.	Spec.	Confounding factors
Breath alcohol	Exhaled air	4–12 hours		97%	93%	Alcohol-containing mouth wash
EtOH	Serum	4–12 hours				
EtG	Urine	Up to 80 hours	>5 g	89%	99%	***Increases*** *results* Accidental contamination of food, mouth wash, alcohol-free beer, etc. with alcohol. UTI ***Decreases*** *results:* Urine dilution deliberately or by diuretics. UTI
EtG	Hair	≤6 months	>20–40 g/d for >3 months	85–92%	87–97%	***Increases*** *results* Seriously impaired renal function EtG containing hair treatment ***Decreases*** *results* Hair treatment: dying, perming, bleaching

EASL CPG ALD. J Hepatol 2018;69:154–81

Alcoholic liver disease

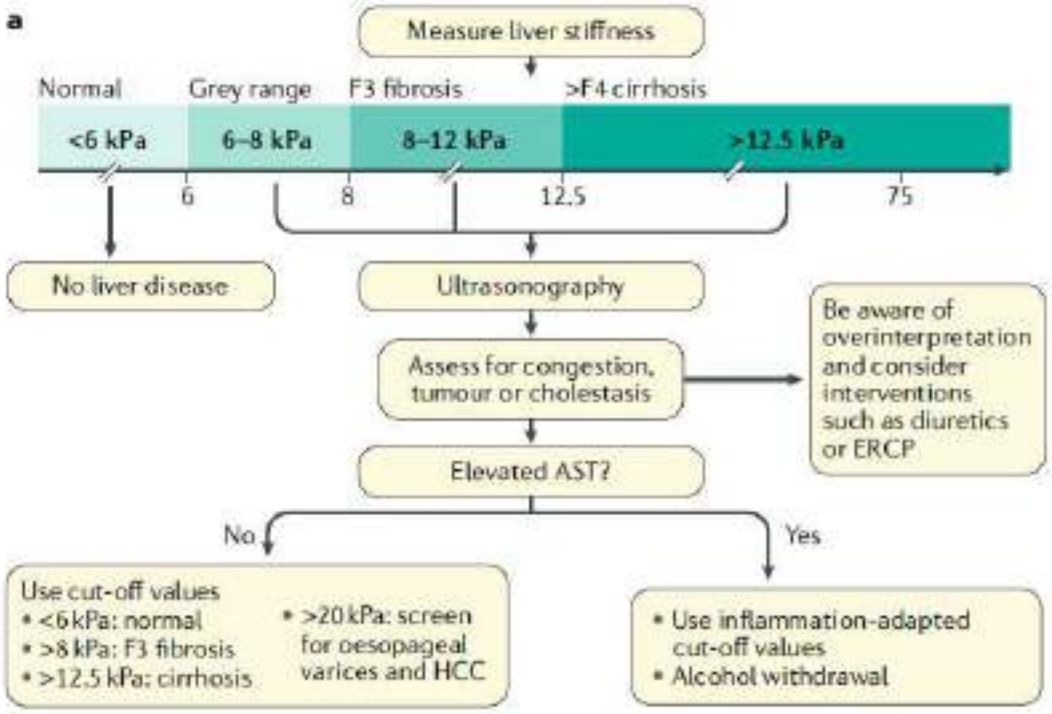
Ultrasonography is useful in detecting fatty infiltration of the liver and determining liver size. The demonstration by ultrasound of portal vein flow reversal, ascites, and intraabdominal collaterals indicates serious liver injury with less potential for complete reversal of liver disease.





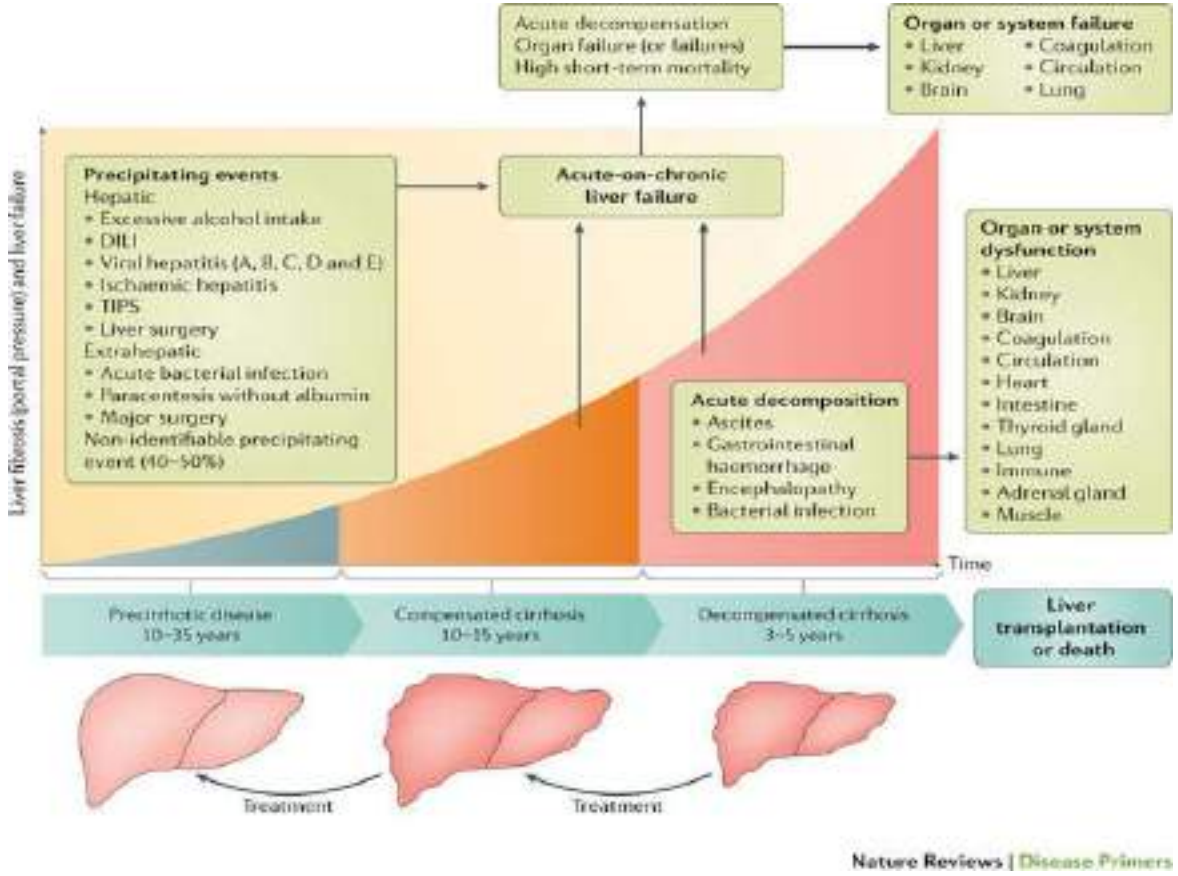
In clinical practice, ultrasonography should be proposed to heavy drinkers as a screening procedure for steatosis . Ultrasonography can also be useful in detecting signs of advanced stages of ALD such as liver cirrhosis, portal-systemic collaterals and splenomegaly

Alcoholic liver disease

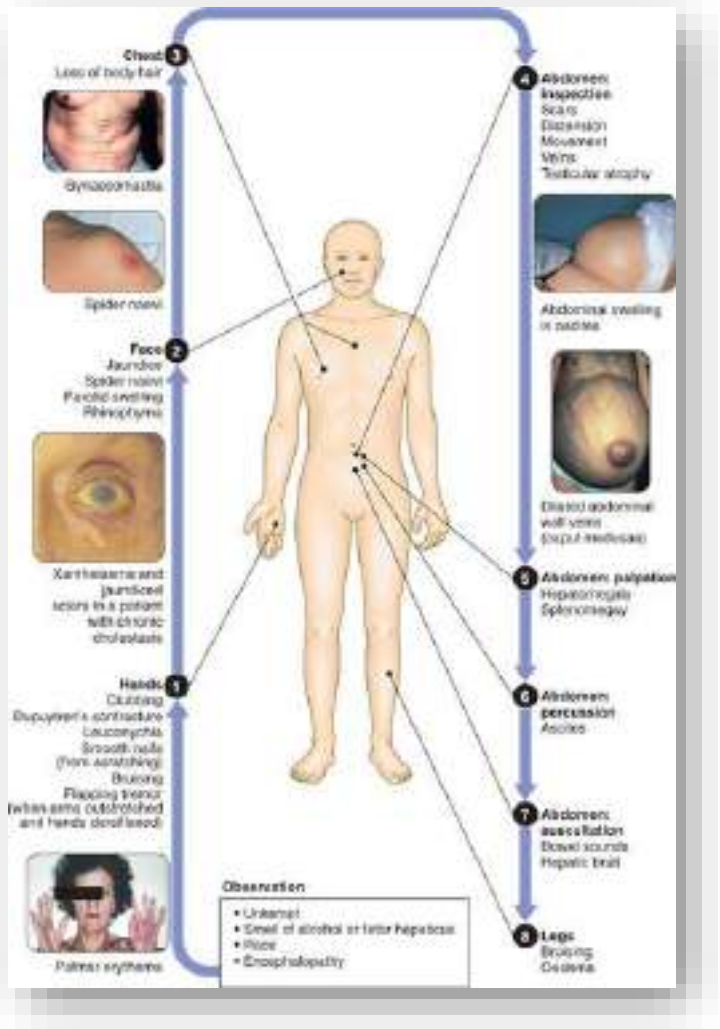


Alcoholic hepatitis

AH should be considered as a clinical syndrome defined by the recent onset of jaundice and/or liver decompensation (i.e. ascites) in a patient with chronic alcohol abuse.



Alcoholic hepatitis

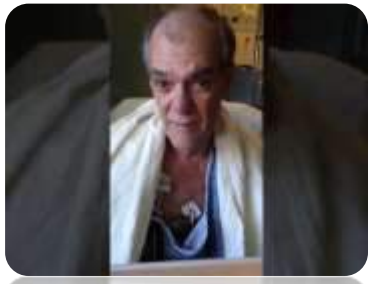


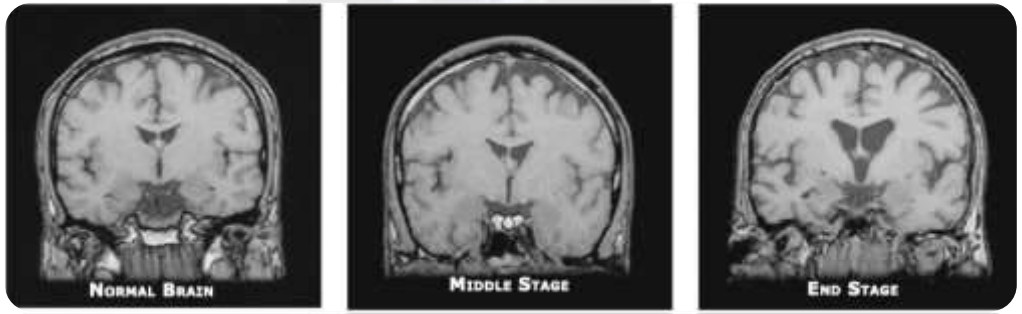
The hallmark of symptomatic AH is the abrupt onset **and/or rapid progression of jaundice**, which may or may not be associated with fever, infection, weight loss, malnutrition, and an enlarged, tender liver.

In severe cases, AH may induce **liver decompensation with ascites, encephalopathy, or gastrointestinal bleeding**.

Patients with severe AH are prone to develop **bacterial infection** and acute renal failure due **to type 1 hepatorenal syndrome**

Wernicke Korsakoff syndrome





WERNICKE-KORSAKOFF SYNDROME

- it is symptom complex of Wernicke disease and the Korsakoff's psychosis .
- Causes of deficiency
  - *1- Chronic alcoholism* (MC) + poor diet
  - *2- Polished rice .*
  - 3-Post gastrectomy
- Pathology : Brain atrophy associated with WKS occurs in the following regions of the brain; the mamillary bodies, the thalamus, the periaqueductal grey, the walls of the 3rd ventricle, the floor of the 4th ventrical, the cerebellum, and the frontal lobe.

WERNICKE-KORSAKOFF SYNDROME

- Eye signs : nystagmus, Ophthalmoplegia , fixed pupils and, rarely, papilloedema .
- Ataxia : broad-based gait, cerebellar signs and vestibular paralysis .
- Cognitive change : amnestic syndrome with confabulation, restlessness, stupor and coma .

Alcoholic hepatitis

Prognosis (1)

Critically ill patients with alcoholic hepatitis have short-term (30 day) mortality rates >50%.

- Severe alcoholic hepatitis is heralded by coagulopathy (prothrombin time > 5 s), anemia, serum albumin concentrations <25 g/L (2.5 mg/dL), serum bilirubin levels > 137 mol/L (8 mg/dL), renal failure, and ascites. A discriminant function calculated as 4.6 x [prothrombin time control (seconds)] + serum bilirubin (mg/dL) can identify patients with a poor prognosis (discriminant function > 32).

Alcoholic hepatitis

Prognosis (2)

Critically ill patients with alcoholic hepatitis have short-term (30 day) mortality rates >50%.

- **The presence of ascites, variceal hemorrhage, severe encephalopathy, or hepatorenal syndrome predicts a dismal prognosis**.
- The pathologic stage of the injury can be helpful in predicting prognosis. Liver biopsy should be performed whenever possible to confirm the diagnosis, to establish potential reversibility of the liver disease, and to guide the therapeutic decisions.

Alcoholic hepatitis

Predicting the evolution

Why is a prognostic score important?

1. Patients with mild disease improve spontaneously upon cessation of alcohol
2. Patients with **severe disease** need a semi-intensive-intensive care
3. Patients with **severe disease** might benefit from initiation of specific therapy

Alcoholic hepatitis

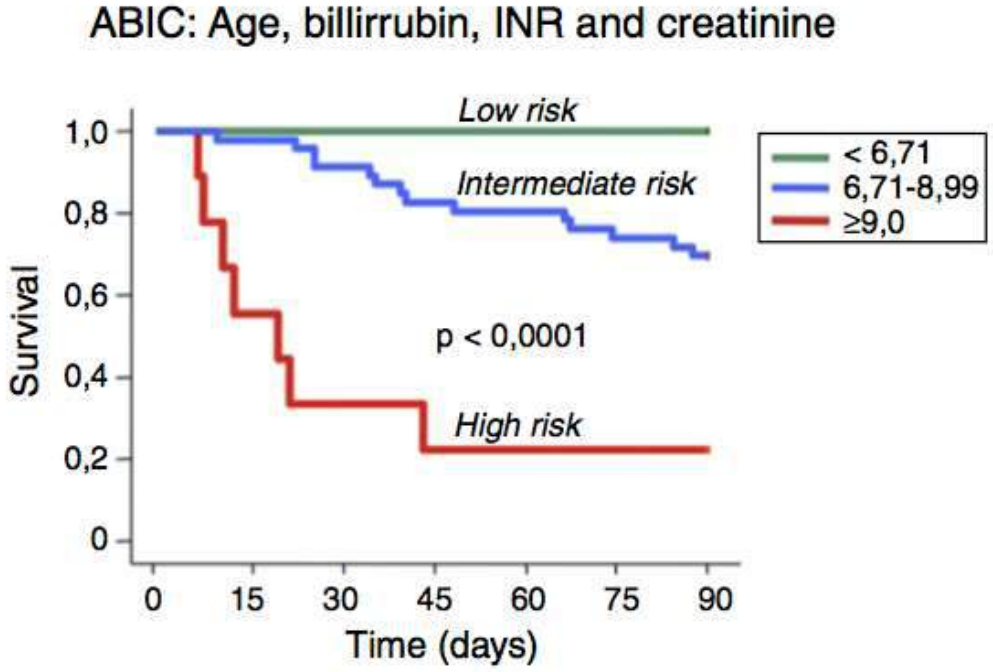
Table I. Prognostic indices for alcoholic hepatitis

Modified Maddrey's discriminant function
DF: 4.6 × [patient prothrombin time − control prothrombin time (seconds)] + bilirubin (mg/dL)

MELD:
3.8 × loge[bilirubin in mg/dL] + 1.2 × loge[INR] + 9.6 × loge[creatinine in mg/dL]

Glasgow index:	*1*	*2*	*3*
Age	< 50	> 50	-
Leukocytes (10⁹/L)	< 15	> 15	-
Urea (mmol/L)	< 5	> 5	-
Prothrombin (ratio)	< 1.5	1.5-2	> 2
Bilirubin (μmol/l)	< 125	125-250	> 250

ABIC Score
(age × 0.1) + (bilirubin × 0.08) + (creatinine × 0.3) + (INR × 0.8)



Alcoholic liver disease

Treatment (1)

Regardless of the severity, abstinence **is the cornerstone of therapy and early management of alcohol abuse or dependence is warranted in all patients with ASH**.

Malnutrition is frequent and nutrition status should be evaluated.

Considering the potential risk of **Wernicke's encephalopathy,** supplementation with B-complex vitamins is recommended. Independent from hepatic encephalopathy, a daily protein intake of 1.5 g/kg of body weight should be ensured.

Liposoluble vitamins (A,D,E K) deficiency should be compensated.

Alcoholic liver disease

Treatment (2)

Patients with symptomatic forms of ASH often develop **acute renal failure which negatively impacts survival.**

The most frequent causes of acute renal failure are Type 1 hepatorenal syndrome.

Severe forms of ASH should be considered as a risk factor of radiocontrast-induced nephropathy.

Measures aimed at preventing the development of renal failure are recommended. They **include volume expansion** if needed and early treatment of hepatorenal syndrome.

Infections are frequent and difficult to diagnose in these patients since SIRS criteria is common at admission and could reflect either the inflammatory state associated with the ASH episode or an ongoing bacterial infection.

Alcoholic hepatitis

Treatment (3)

Patients with severe alcoholic hepatitis, **40 mg/d, or prednisolone**, for 4 weeks followed by a steroid taper. Exclusion criteria included active gastrointestinal bleeding, sepsis, renal failure, or pancreatitis.

Women with encephalopathy from severe alcoholic hepatitis may be particularly good candidates for glucocorticoids.

TNF inhibition as an alternative to glucocorticoids for severe alcoholic hepatitis. The nonspecific **TNF inhibitor, pentoxifylline,** recently demonstrated improved survival in the therapy of severe alcoholic hepatitis

Alcoholic hepatitis

Treatment (4)

Most studies indicate that only a limited proportion of patients with severe forms of ASH benefit from corticosteroids.

Thus, early identification of non-responders to corticosteroids is important to define stopping rules and limit unnecessary exposure.

For example, after 7 days on corticosteroids, **a Lille score above 0.45 predicts poor** response.

In poor responders, the interruption of corticosteroids is recommended particularly in those classified as null responders (Lille score >0.56).

In poor responders, an early switch to pentoxifylline or the use of a molecular adsorbent recirculating system (MARS) appears not to modify the outcome.

In these patients, early liver transplantation may be considered after a careful selection process.

Alcoholic hepatitis

Treatment (5)

Liver transplantation (1)

- The idea that alcoholism is self-inflicted must be reconciled with the strong evidence supporting genetic and environmental influences on alcohol dependence diagnosed by the DSM-IV diagnostic system.
- Graft and patient survival rates among alcoholics after LT are similar to those seen after transplantation for other aetiologies of liver disease.
- A significant increase in the proportion of patients transplanted for alcoholic liver disease was observed between the periods 1988–1995 and 1996–2005 in Europe

Alcoholic hepatitis

Treatment (5)

Liver transplantation (3)

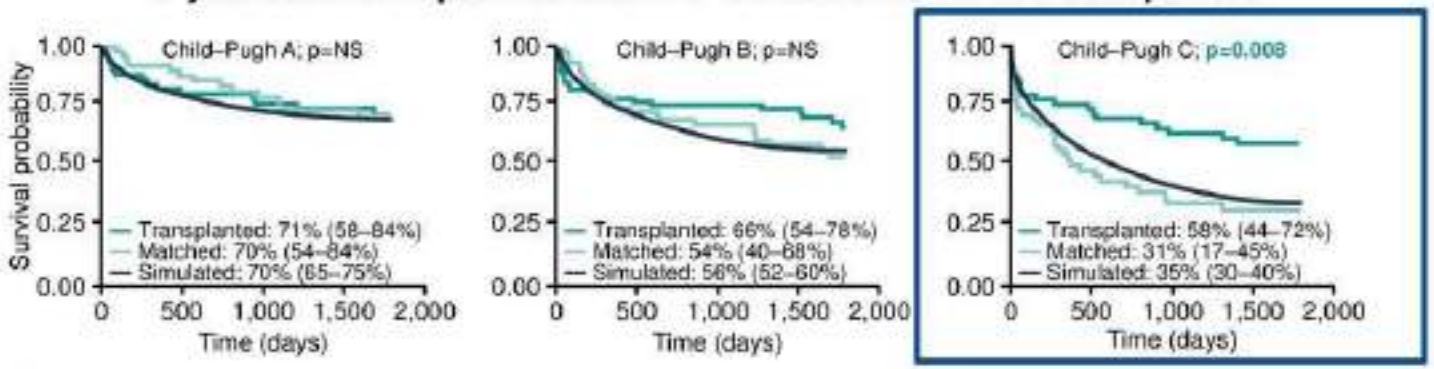
- In Child–Pugh stage B alcoholic cirrhosis, immediate listing for LT did not show a survival benefit compared with standard care.
- In most centers, the MELD score is mainly used to prioritize patients awaiting LT .
- Previous studies have failed to demonstrate that other clinical manifestations of liver decompensation, such as variceal hemorrhage, hepatic encephalopathy, new onset ascites or spontaneous bacterial peritonitis, were independent predictors of survival over and above the MELD score. **Nonetheless, the onset of any of these features in an abstinent alcoholic should prompt the managing physician to consider referral to a transplant center.**

Alcoholic hepatitis

Liver transplantation: Selection of patients for LT

- Survival benefit related to LT is restricted to patients with **advanced** decompensation

5-year survival in patients with ALD cirrhosis: LT vs. non-transplanted[1]

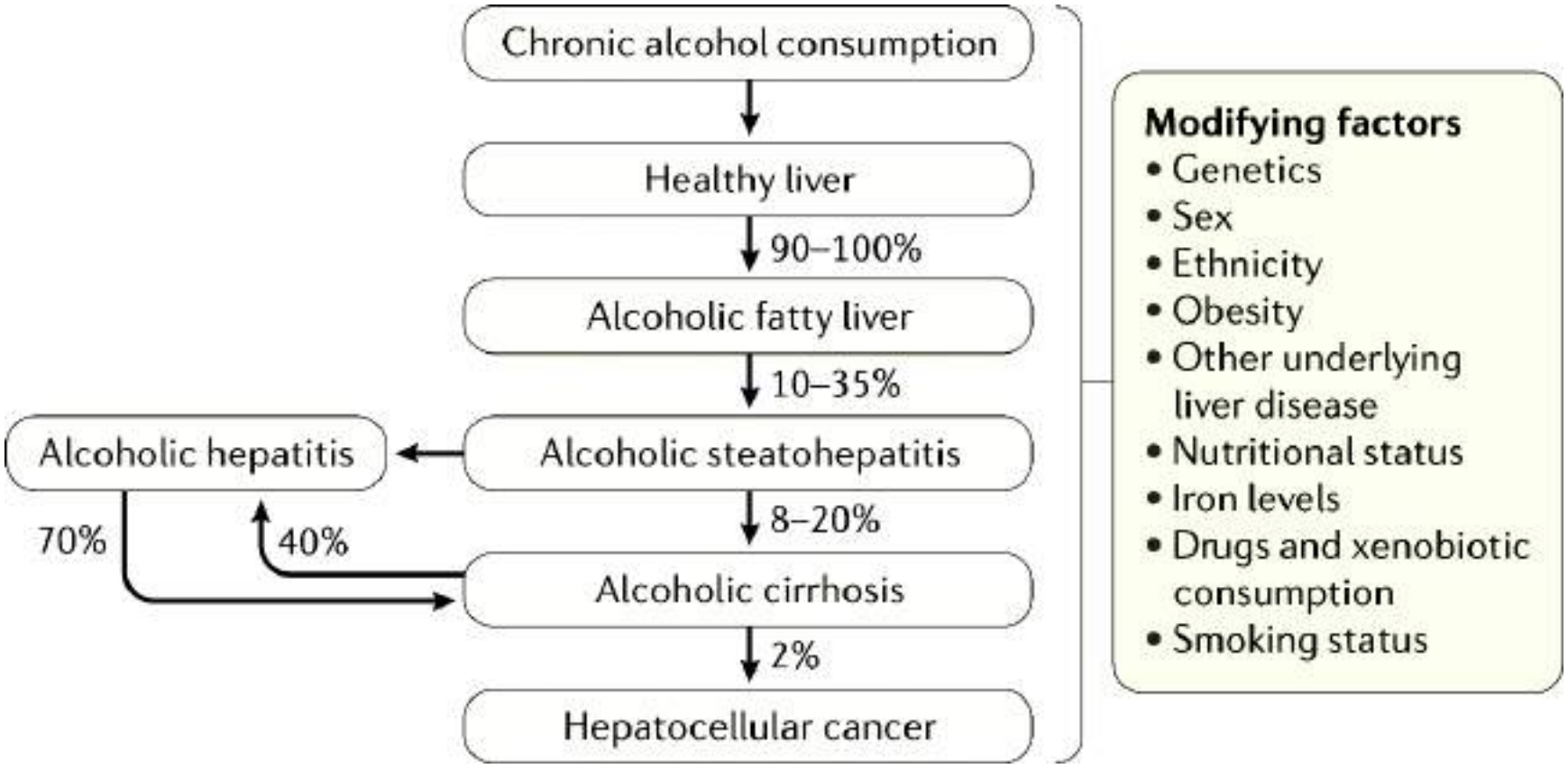


- MELD accurately estimates the survival benefit following LT
  - Generally recommended to prioritize organ allocation
- Clinical manifestations of liver decompensation are not independent predictors of survival over and above MELD
  - Onset in an abstinent patient should prompt consideration of referral to a transplant centre
- Increasing evidence of the benefit of early LT in for patients with severe AH not responding to medical therapy
  - Selection criteria for such patients need to be more clearly defined

1. Poynard T, et al. J Hepatol 1999;30:1130–7;
EASL CPG ALD. J Hepatol 2018;69:154–81

EASL

Alcoholic liver disease



Alcoholic liver cirrhosis

- When fibrosis reaches a certain degree, there is disruption of the normal liver architecture and **replacement of liver cells by regenerative nodules**. In alcoholic cirrhosis, the nodules are usually **<3 mm in diameter**; this form of cirrhosis is referred to as **micronodular**.
- With cessation of alcohol use, larger nodules may form, resulting in a **mixed micronodular and macronodular cirrhosis**