Fatty Liver and Insulin Resistance

Msc Zoology (2nd Semister)

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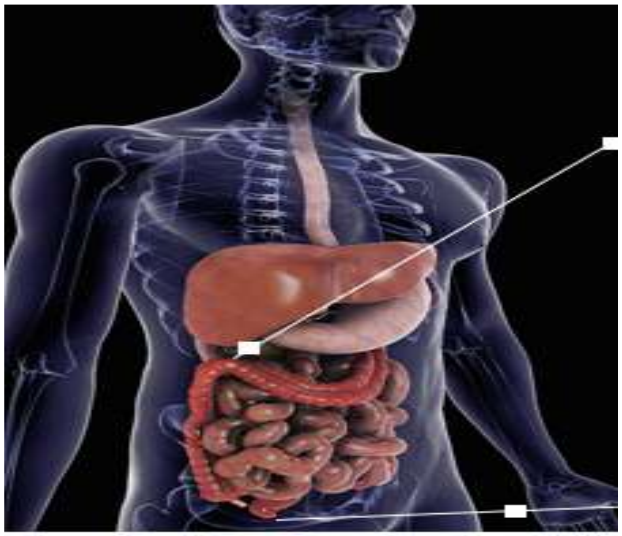
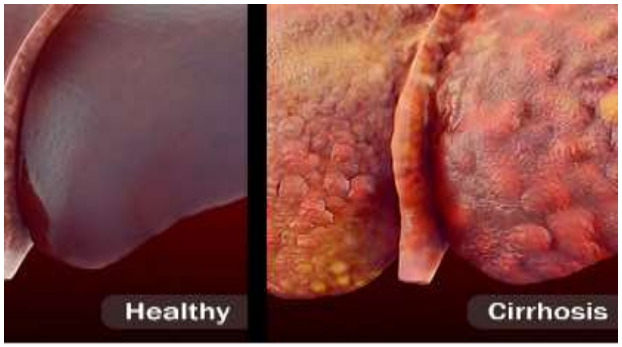
OIST

Liver

Weighing between 3.17 and 3.66 pounds (lb), or between 1.44 and 1.66 kilograms (kg), the liver is reddish-brown with a rubbery texture. It is situated above and to the left of the stomach and below the lungs.





Major Function of Liver (500)

- :
- **Bile production:** Bile helps the small intestine break down and absorb fats, cholesterol, and some vitamins. Bile consists of bile salts, cholesterol, bilirubin, electrolytes, and water.
- **Absorbing and metabolizing bilirubin:** Bilirubin is formed by the breakdown of hemoglobin. The iron released from hemoglobin is stored in the liver or bone marrow and used to make the next generation of blood cells.
- **Supporting blood clots:** Vitamin K is necessary for the creation of certain coagulants that help clot the blood. Bile is essential for vitamin K absorption and is created in the liver. If the liver does not produce enough bile, clotting factors cannot be produced.
- **Fat metabolization:** Bile breaks down fats and makes them easier to digest.
- **Metabolizing carbohydrates:** Carbohydrates are stored in the liver, where they are broken down into glucose and siphoned into the bloodstream to maintain normal glucose levels. They are stored as glycogen and released whenever a quick burst of energy is needed.
- **Vitamin and mineral storage:** The liver stores vitamins A, D, E, K, and B12. It keeps significant amounts of these vitamins stored. In some cases, several years' worth of vitamins is held as a backup. The liver stores iron from hemoglobin in the form of ferritin, ready to make new red blood cells. The liver also stores and releases copper.
- **Helps metabolize proteins:** Bile helps break down proteins for digestion.
- **Filters the blood:** The liver filters and removes compounds from the body, including hormones, such as estrogen and aldosterone, and compounds from outside the body, including alcohol and other drugs.
- **Immunological function:** The liver is part of the mononuclear phagocyte system. It contains high numbers of Kupffer cells that are involved in immune activity. These cells destroy any disease-causing agents that might enter the liver through the gut.
- **Production of albumin:** Albumin is the most common protein in blood serum. It transports fatty acids and steroid hormones to help maintain the correct pressure and prevent the leaking of blood vessels.
- **Synthesis of angiotensinogen:** This hormone raises blood pressure by narrowing the blood vessels when alerted by production of an enzyme called renin in the kidneys.

Growth Factors Regulate Liver Function and Growth

- hepatocyte growth factor
- insulin
- transforming growth factor-alpha
- epidermal growth factor
- interleukin-6
- norepinephrine
-

Recent Findings on Fatty Liver

- Hyötyläinen T. Et al. (2016) **Genome-scale study reveals reduced metabolic adaptability in patients with non-alcoholic fatty liver disease.**
- *Nat. Commun.* **7**: 8994.

- **Grohmann et al. (2018)**
- Drives STAT-1-Dependent NASH and . STAT-3-Dependent HCC.

- *Cell,* October 25, 2018

What is Fatty Liver?

20-30% American have NAFLD?

2-5% have NASH

25% have Fatty Liver?

80% Obese People have NAFLD?

Fatty Liver: Fat enters the liver cell. Next the cell swells and changes which causes liver injury.

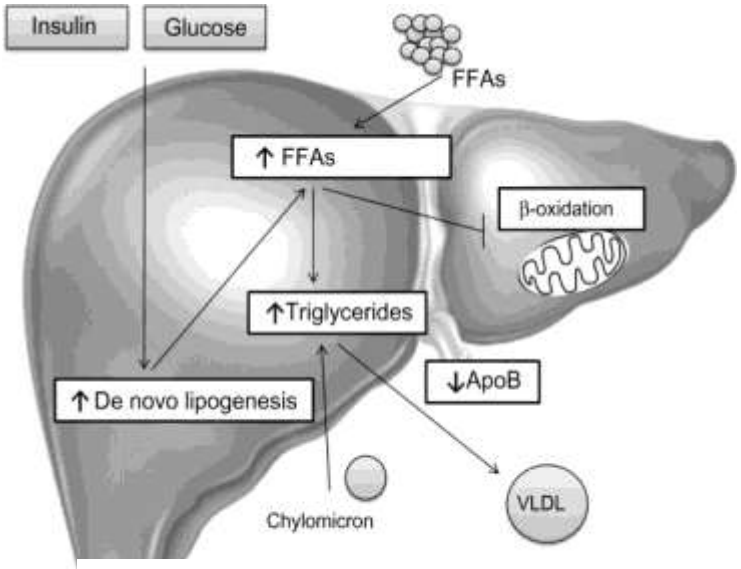
NASH: A bad case of liver injury which can progress to cirrhosis or severe scarring of the liver. Not everyone with NASH will develop cirrhosis.

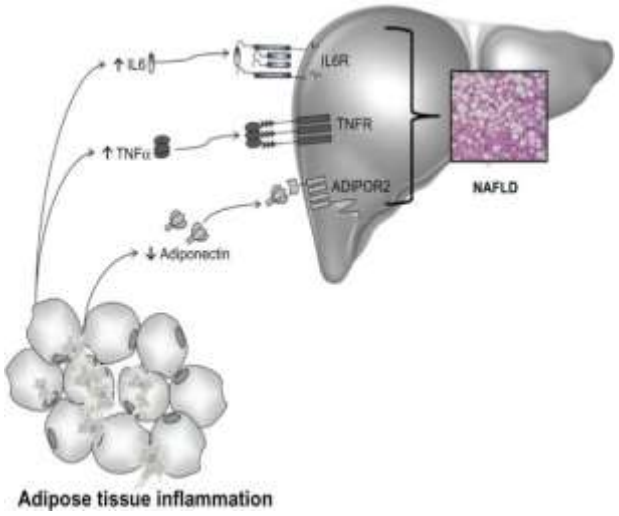
Cirrhosis: A scarred liver from years of damage.

Sign of NAFLD

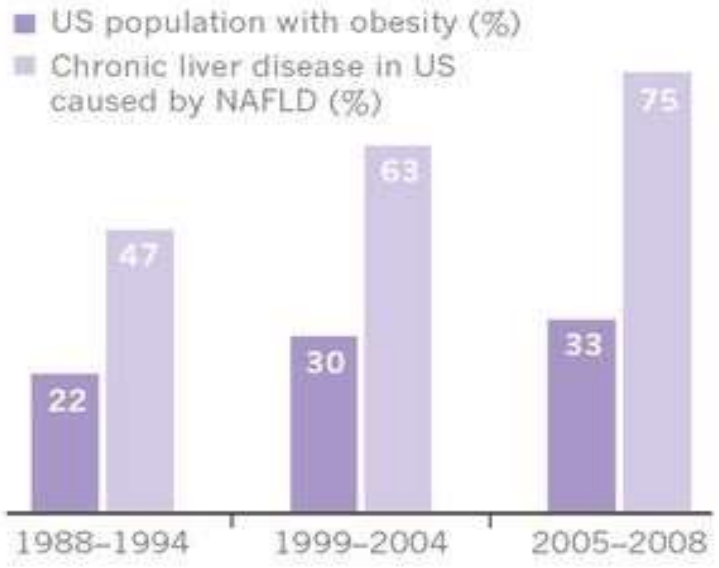
- 1. No sign
- 2. Tired
- 3. Pain-right upper abdomen
- 4. Jundice
- 5. Enlarged liver
- 6. Obesity
- Weight loss
- Fluid in the abdomen
- Insulin Resistance
- Dislipidemia
- High TG and LDL
- PCOS

NAFLD

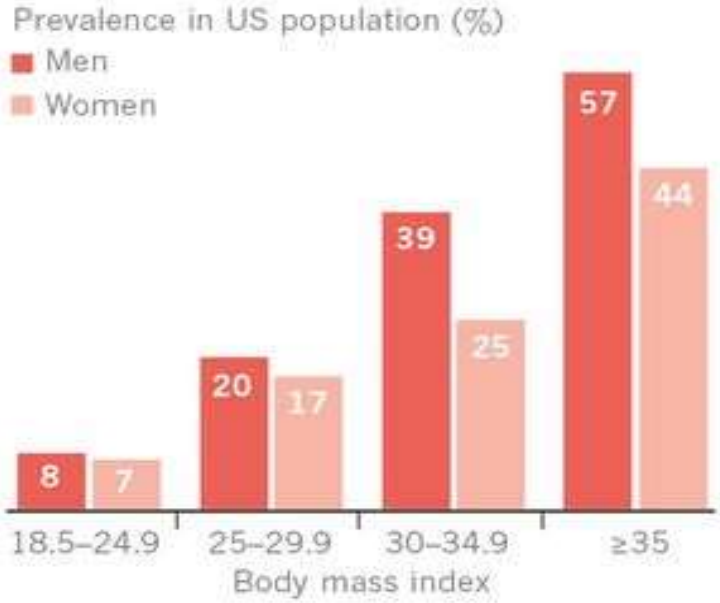




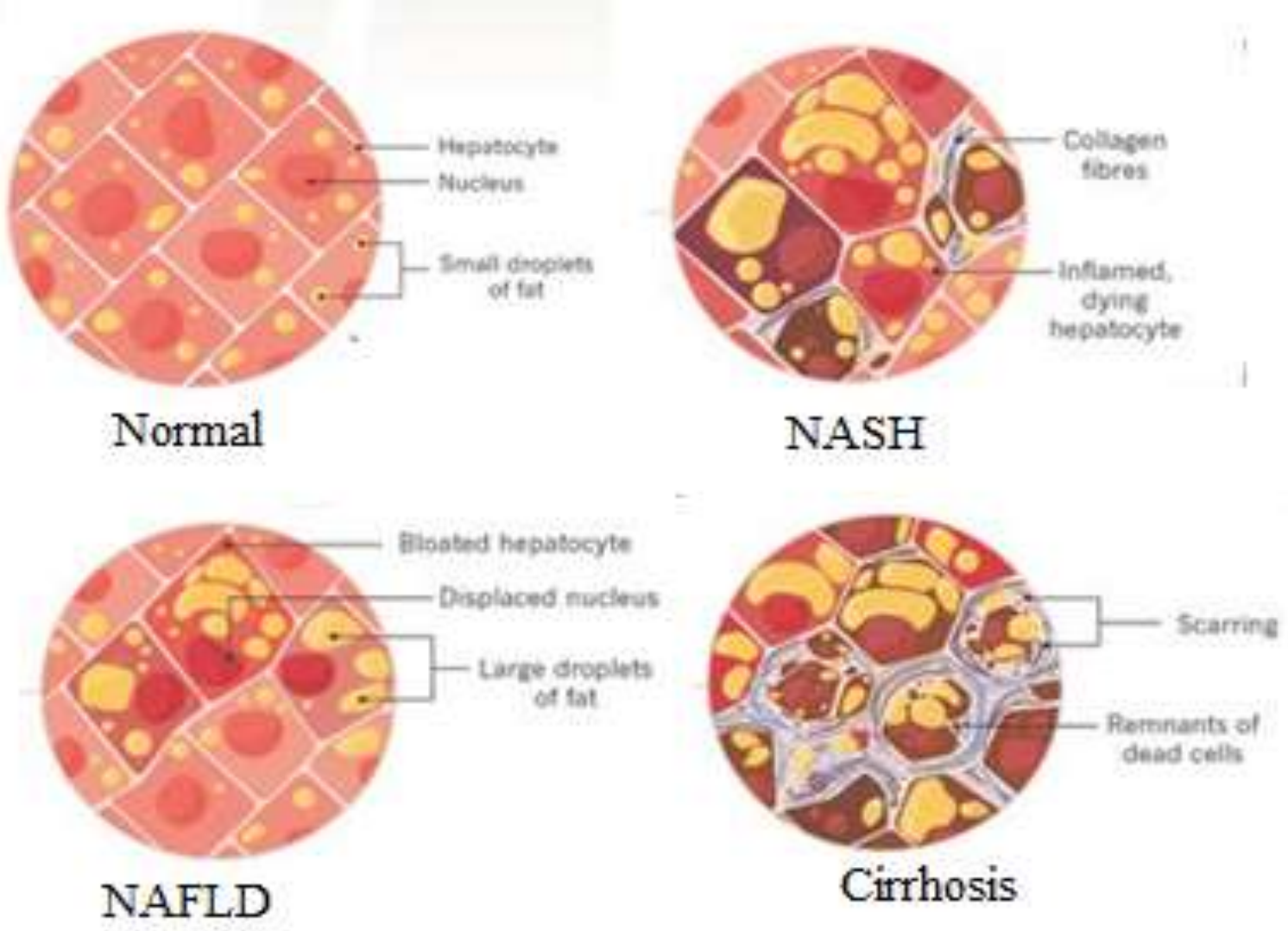
As levels of obesity have increased, so too has the prevalence of NAFLD[4].



NAFLD increases in prevalence with body mass index, and is more common in men[5].



Fighting the fatty liver; Dr. Liam Drew;
Nature **550**, S102–S103, 2017.



Ultra-Sonography and CT-Scan

Tallino, S et al. (2015) Nutrigenomics analysis reveals that copper deficiency and dietary sucrose upregulate inflammation, fibrosis andlipogenic pathwaysin a mature rat model of nonalcoholic fatty liver disease. J. Nutr. Biochem. 26, 996–1006

Copper absorption, distribution, and metabolism: copper enters the enterocytes through CTR1 and flows out in the portal circulation by ATP7A. In the liver, Cu has a key role in defense against ROS (binds SOD) and in mitochondrial respiration. Linked to CP, copper is brought in the bloodstream to be transported to other tissues and organs. ATP7B ensures copper transport across the membranes of cellular organelles or allows for excess copper to be excreted into the bile. Cu: copper; CTR1: copper transporter protein-1; CCS: copper chaperone of superoxide dismutase; COX: cytochrome-C oxidase; Sco1, Sco2: cytochrome c oxidase assembly factors; Cu/Zn SOD: copper-zinc-dependent superoxide dismutase; ATP7A/B

FALD and NAFLD

Nonalcoholic fatty liver disease (NAFLD) is a disorder characterizedby excess accumulation of fat in hepatocytes. A subset of patients will develop progressive fibrosis, which can progress to cirrhosis. Hepatocellular carcinoma and cardiovascular complications are life-threatening co-morbidities of both NAFLD and NASH.

- Alcoholic steatohepatitis (NASH) including steatosis, inflammation, hepatocyte balloon (a type of hepatocyte injury), Mallory–Denk bodies
- (Mallory hyaline) and fibrosis within the lobules. NAFLD is closely associated with insulin resistance; obesity and metabolic syndrome are common underlying factors .

Precautions

Fact today

- Nonalcoholic fatty liver disease (NAFLD) and diabetes are common metabolic disorders whose prevalence rates are expected to rise worldwide, corresponding to aging and increasingly obese populations.
- Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide and is associated with hepatocellular carcinoma (HCC), the most frequent malignant liver tumor.

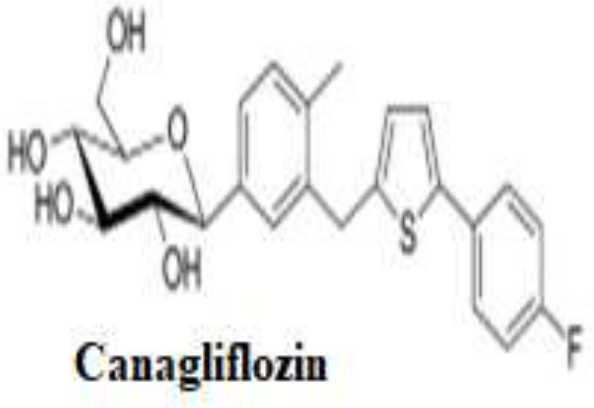
Hope

Soluble epoxide hydrolase (sEH) hydrolyzes epoxyeicosatrienoic acids (EETs) and other epoxy fatty acids, attenuating their cardiovascular protective effects.

Treatment with a highly selective specific sEH inhibitor (0.8 mg/kg/day for the animal model and 1 μM for cells) prevented HHcy-induced lipid accumulation in vivo and in vitro.

Hope

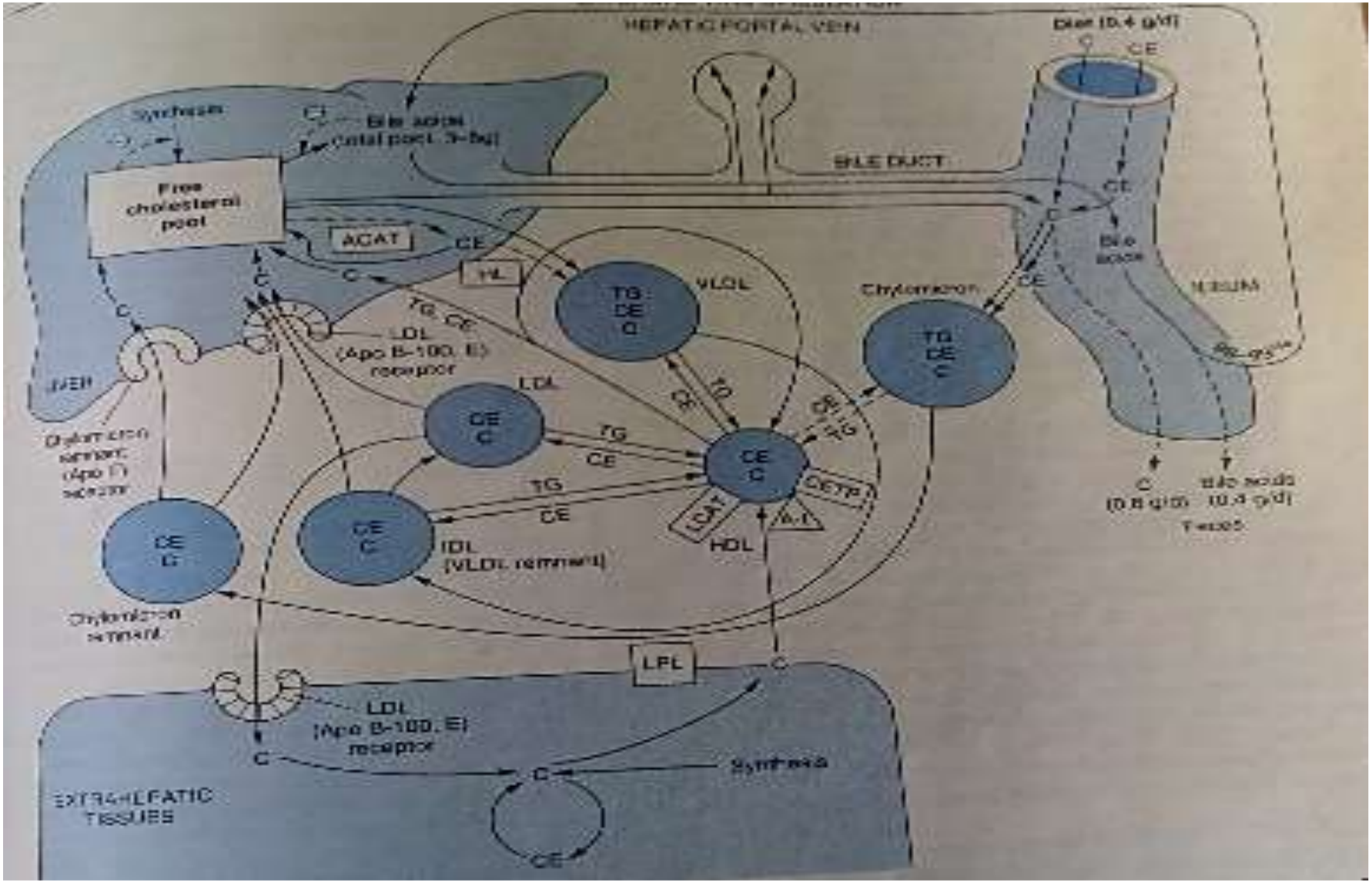
Sodium glucose co-transporter-2 (SGLT-2) help to enter glucose into cells for glycolysis.



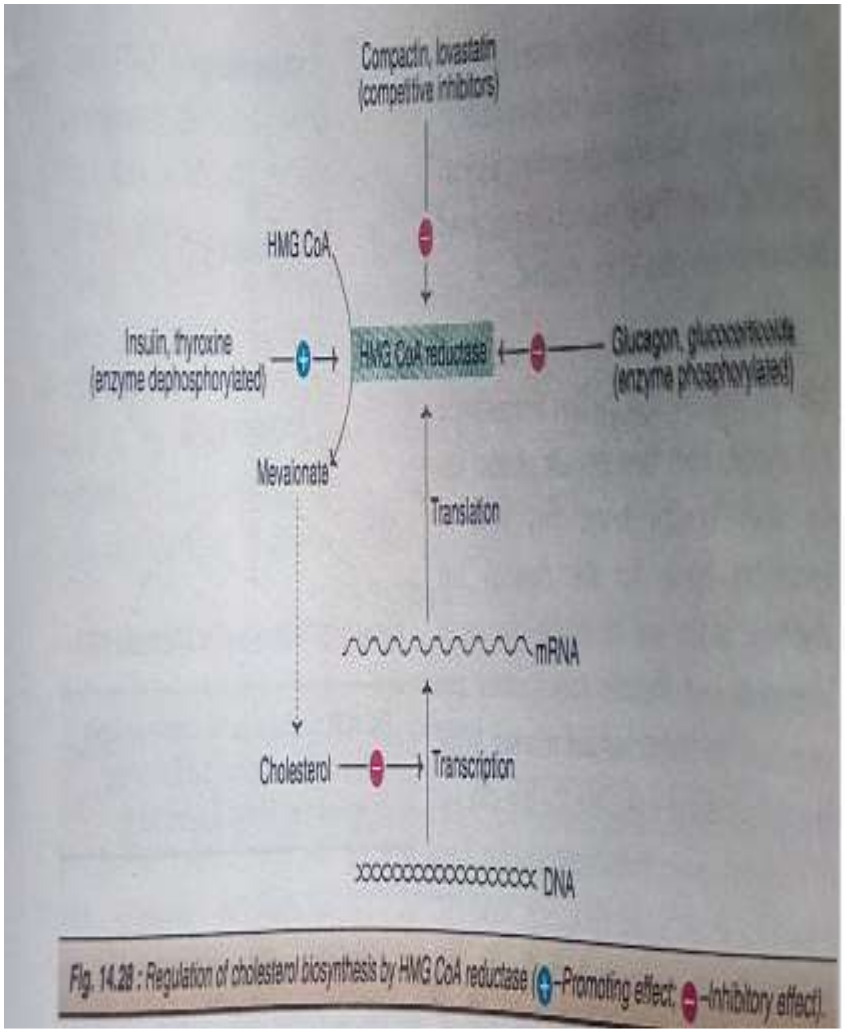
Canagliflozin

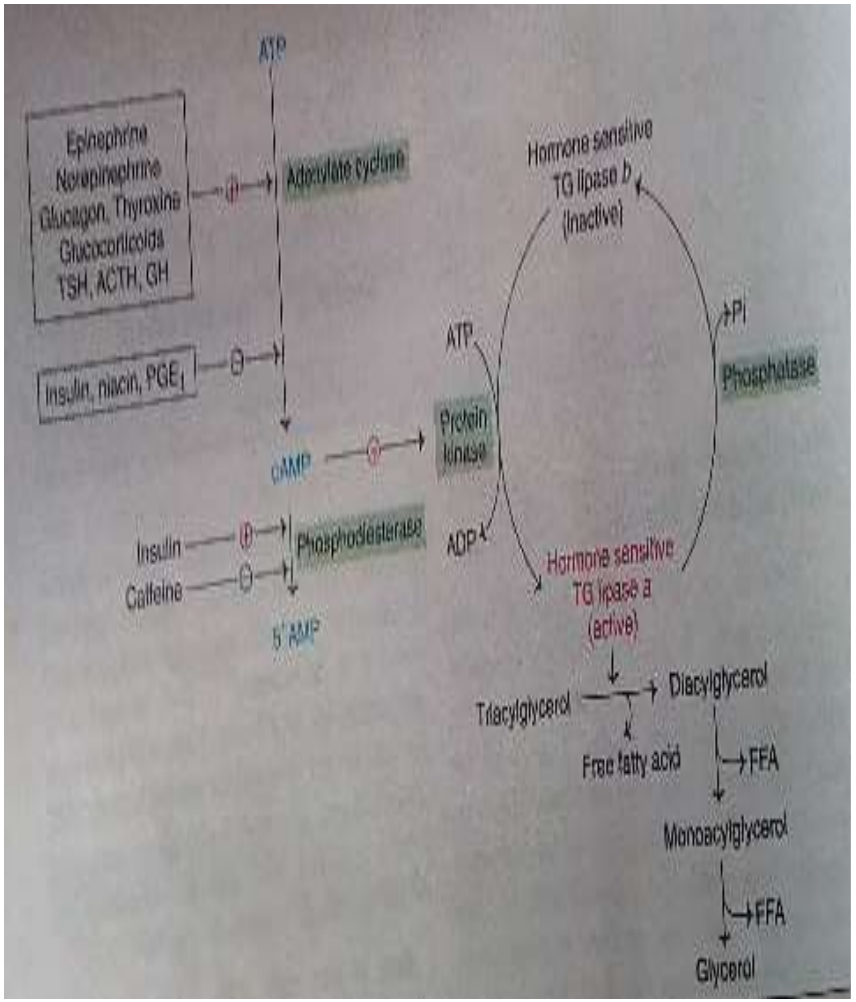
- Five studies reported a a significant reduction in hepatic fat content in those treated with SGLT-2 inhibitors,like canaglifozin.

Fat and Fatty acids transport

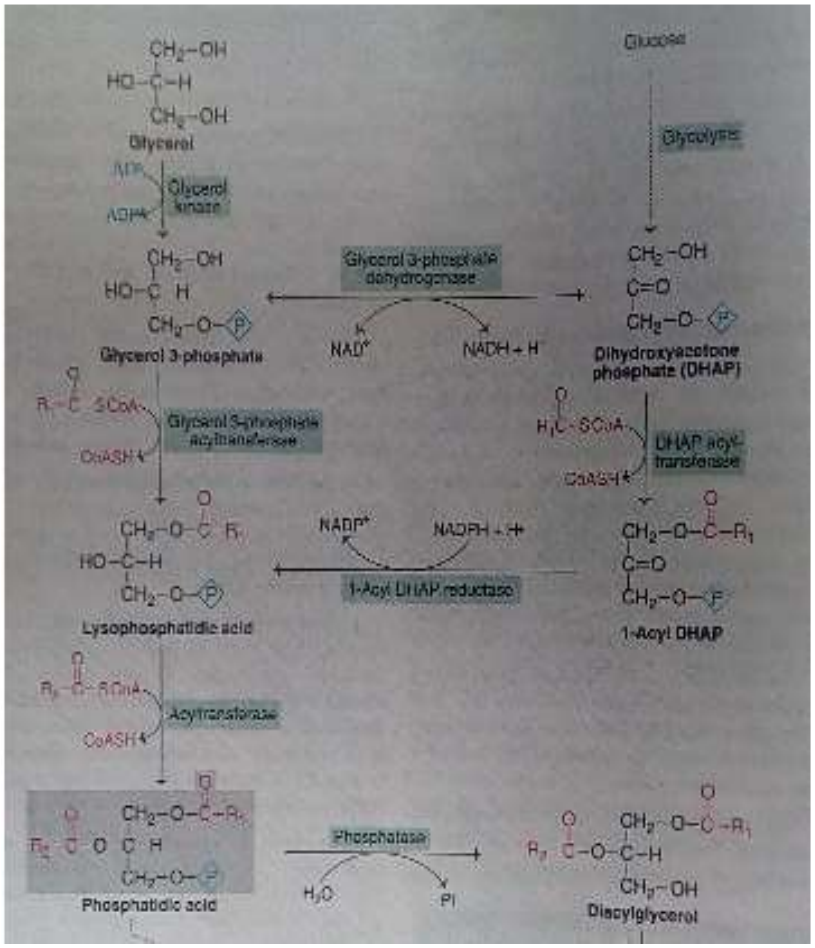


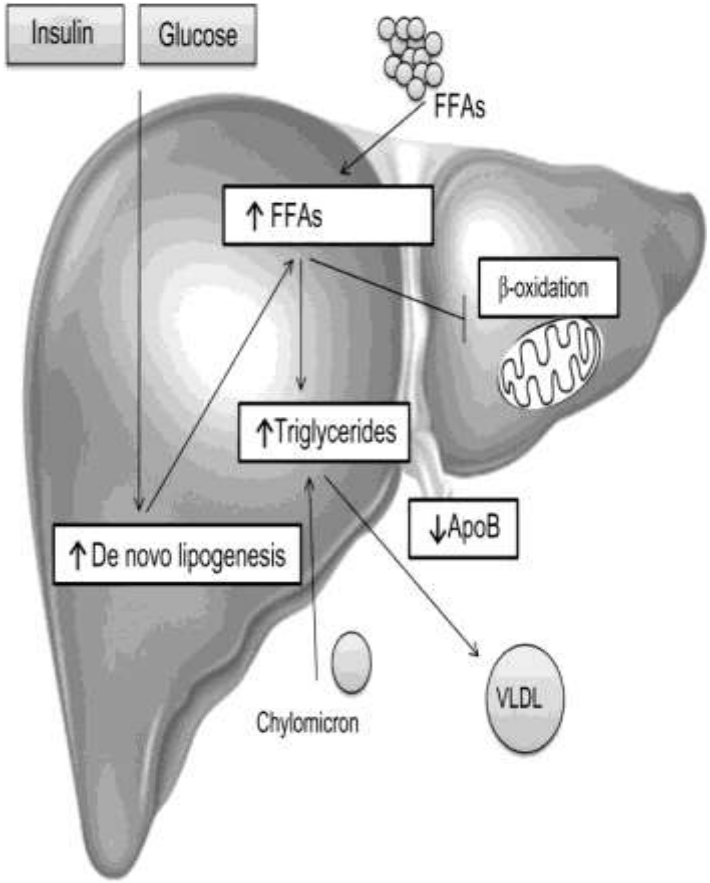
Regulation fat synthesis





New Targets to control Fat Metabolism



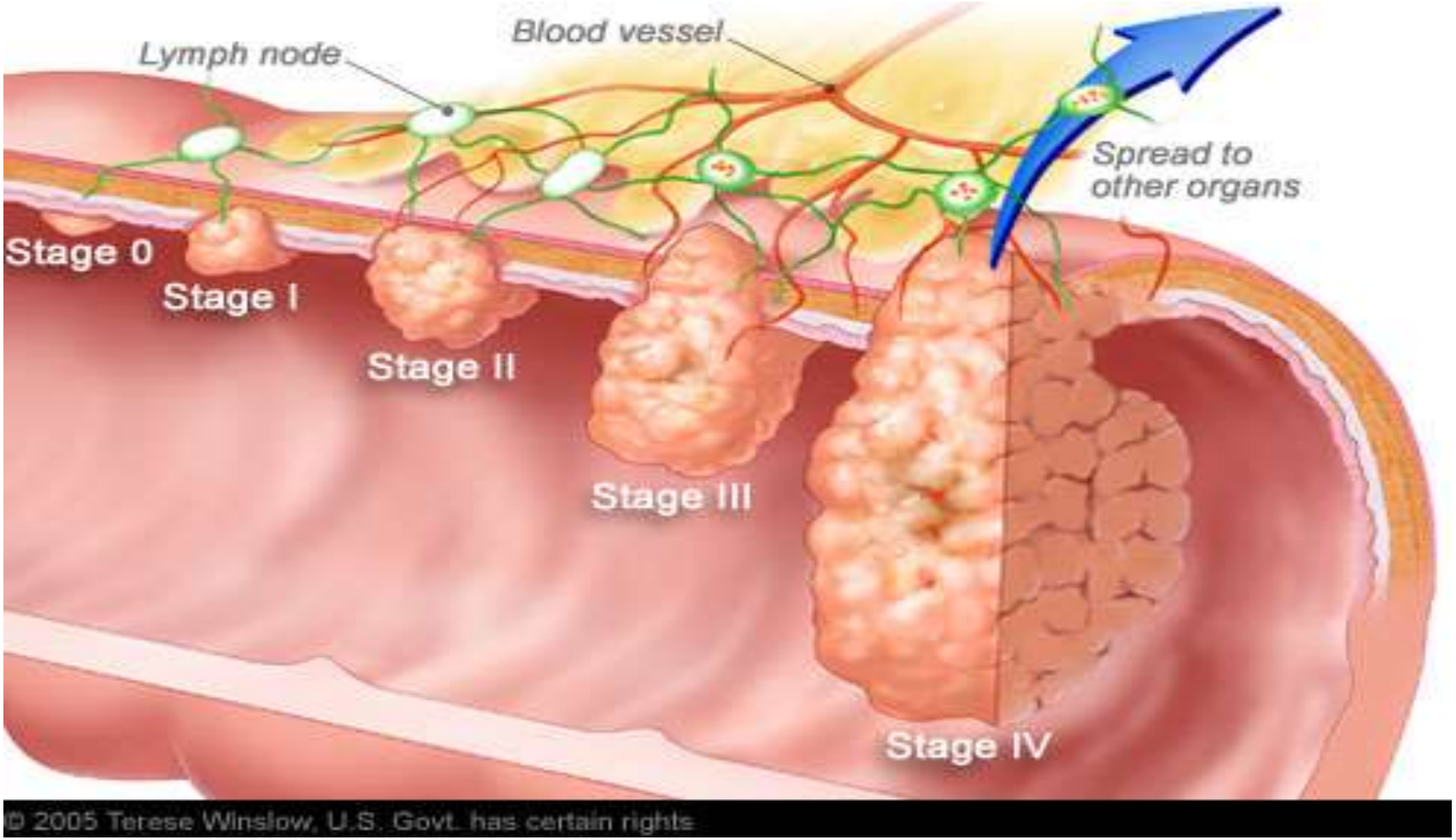


Diseases of Fat Metabolism

Table 14.4 Some examples of sphingolipidoses (lipid storage diseases) with their characteristics

Disease	*Missing/defective enzyme*	*Major storage compound*	*Symptoms*
Niemann-Pick disease	Sphingomyelinase	Sphingomyelins	Enlargement of liver, spleen, mental retardation.
Farber's disease	Ceramidase	Ceramide	Painful and deformed joints.
Gaucher's disease	β-Glucosidase	Glucocerebroside	Enlargement of liver and spleen, osteoporosis, mental retardation.
Krabbe's disease	β-Galactosidase	Galactocerebrosides	Absence of myelin formation, liver and spleen enlargement, mental retardation.
Tay-Sachs disease	Hexosaminidase A	Ganglioside GM_2	Blindness, mental retardation, death within 2-3 years.
Fabry's disease	α-Galactosidase	Ceramide trihexoside	Renal failure, skin rash, pain in lower extremities.

Colorectal Cancer



Questions

- What is fatty acid synthase? Outline its function.
- When fatty acid beta-oxidation occurs and how?
- Describe NAFLD and give reason for it.
- How you link fatty liver and liver cancer?
- Describe the development of drugs for fatty liver and liver cancer.
- Write the reason of omega fatty acid supplement necessary.
- Write the structure of arachidonic acid and names the important metabolic products.
- Describe the role of insulin and Glu-2/4 transporters in insulin resistance and fatty liver generation.
- Write three essential facts to do daily to prevent fatty liver.