بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | Final 12

Metabolism of cholesterol pt.2

Lipid soluble vitamins

Written by : DST

Reviewed by : NST

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: العلي الأعلى القهار، الذي تنفذ مشيئته في خلقه، وهو الرؤوف الجابر للقلوب المنكسرة، وللضعيف العاجز، ولمن لاذ به ولجأ إليه.

الورود: ورد مرة واحدة في القرآن.

الشاهد: ﴿ٱلْعَزِيزُ ٱلْجَبَّارُ ٱلْمُتَكَبِّرُ﴾ [الحشر:٢٣].

اضغط هنا لشرحٍ أكثر تفصيلًا

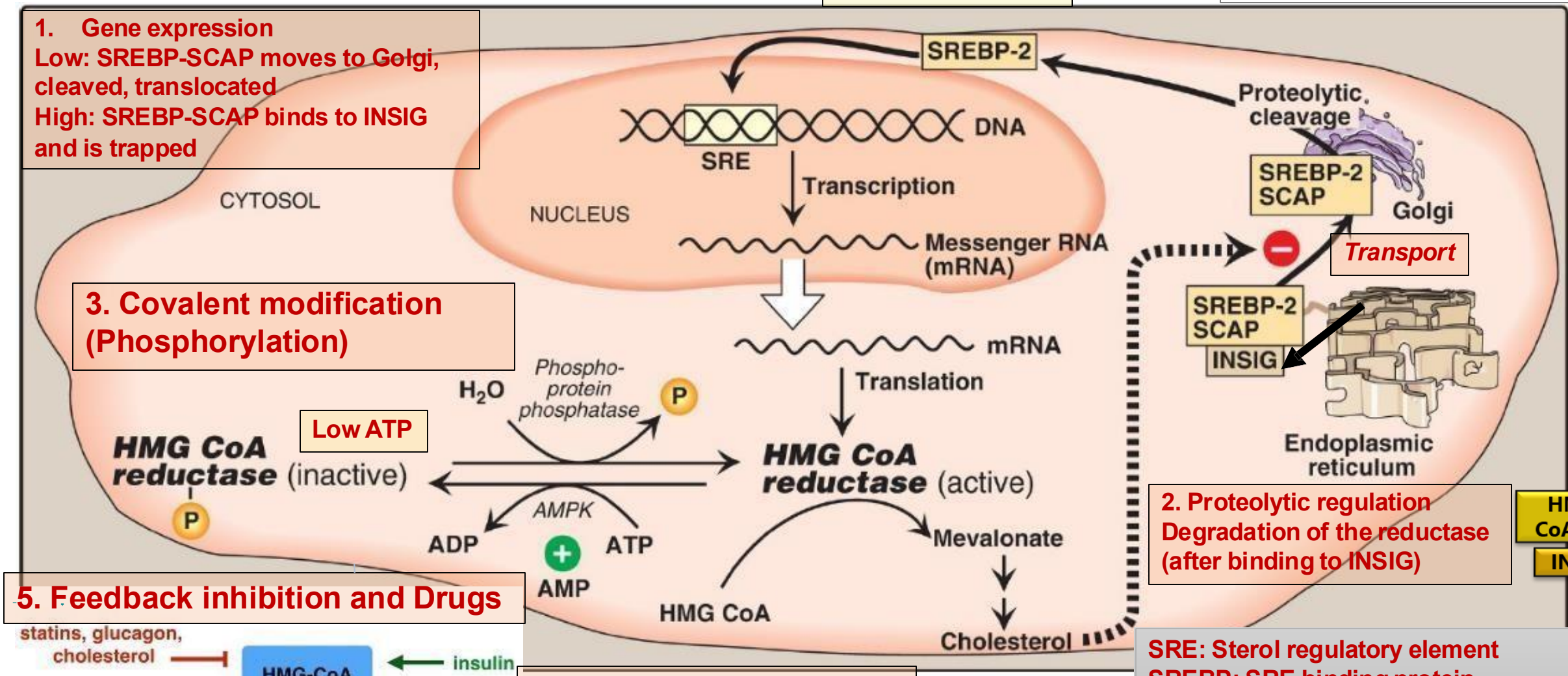
Regulation of cholesterol synthesis

Refer back to the lecture for more understanding:)

For explanation, refer to the next slides

↑ HMG CoA reductase
↑ FA synthesis enzymes

1. Gene expression
Low: SREBP-SCAP moves to Golgi, cleaved, translocated
High: SREBP-SCAP binds to INSIG and is trapped



3. Covalent modification (Phosphorylation)

2. Proteolytic regulation
Degradation of the reductase (after binding to INSIG)

HMG-CoA red.
INSIG

5. Feedback inhibition and Drugs

statins, glucagon, cholesterol → HMG-CoA reductase ← insulin

4. Hormonal regulation
(through phosphatase and PKA)

SRE: Sterol regulatory element
SREBP: SRE binding protein
SCAP: SREBP cleavage–activating protein
INSIG : Insulin-induced gene proteins

Regulation of cholesterol synthesis

Regulation typically occurs at irreversible reactions.

One of the key enzymes involved in the regulation of cholesterol synthesis is **HMG-CoA reductase**, which is controlled through various mechanisms, including:

1. **Gene Expression Regulation**:The regulation of HMG-CoA reductase can occur at the levels of transcription, translation, and protein synthesis, depending on whether the cell needs more of the enzyme. A key player in this process is Sterol Response Element Binding Protein **(SREBP-2)**, which controls gene expression.

SREBP-2 activates the transcription of cholesterol-related genes, including the HMG-CoA reductase gene, fatty acid synthase , acetyl co- carboxylase , by binding to specific DNA sequences called Sterol Response Elements (SRE) in the nucleus. This increases the enzyme's concentration, leading to enhanced cholesterol synthesis.

Under normal conditions, SREBP-2 remains inactive when bound to two proteins: **SCAP** and **INSIG**, forming a complex in the **endoplasmic reticulum (ER)**. If there is no need for cholesterol synthesis, this complex remains in the ER. When a stimulus for cholesterol synthesis occurs, **INSIG** detaches, activating the remaining SCAP-SREBP-2 complex.

SRE: Sterol regulatory element SREBP: SRE binding protein SCAP: SREBP cleavage-activating protein
INSIG : Insulin-induced gene proteins

Regulation of cholesterol synthesis

2. Proteolytic Cleavage: This complex is then transported to the **Golgi apparatus**, where **proteolytic cleavage** releases active SREBP-2. The free SREBP-2 enters the nucleus to stimulate gene expression (HMG CO A reductase , fatty acid synthase, Acetyl CO A carboxylase) thereby promoting cholesterol synthesis.

3. Covalent modulation (phosphorylation) : HMG-CoA reductase is regulated through phosphorylation. Hormones like **glucagon** and **epinephrine**, which act during fasting conditions, bind to their respective **GPCRs** (G protein-coupled receptors). This binding activates protein kinase A (PKA) and **AMP-activated kinase** (AMPK), which phosphorylate HMG-CoA reductase, thereby inhibiting its activity (as previously mentioned, cholesterol synthesis primarily occurs in the fed state, not during fasting conditions).

4. Hormoal Regulation: insulin activates phosphates enzyme that removes the phosphate group from HMG-CoA reductase, activating it and promoting cholesterol synthesize.

5. Feedback inhibition and Drugs:

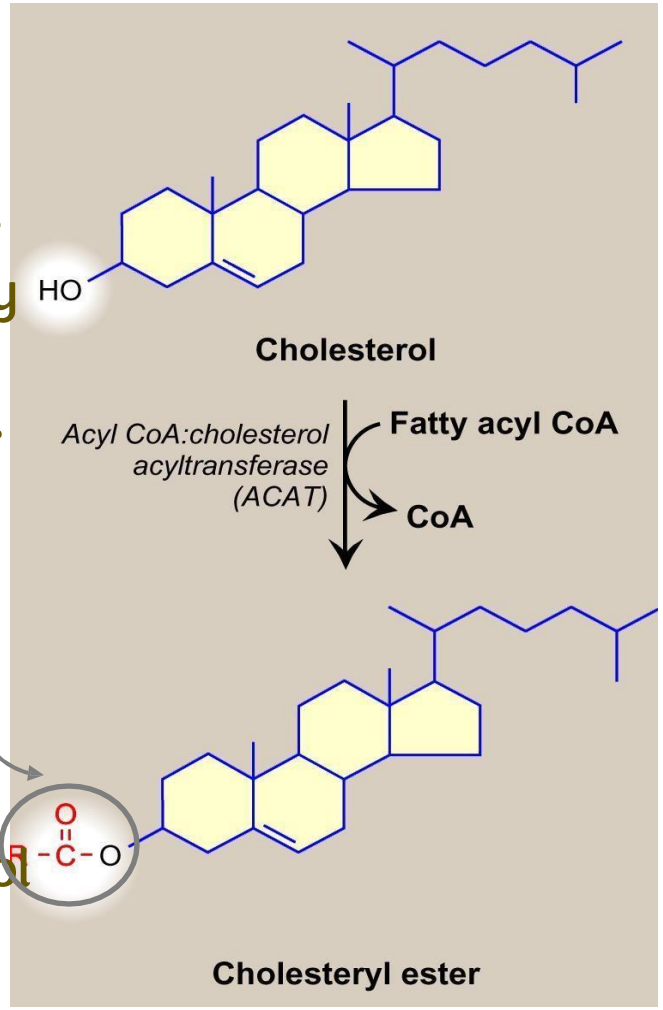
a. When cholesterol levels are high, it inhibits **HMG-CoA reductase** and prevents the transport of the **SREBP-2-SCAP** complex to the Golgi apparatus.
b. Statins are a group of drugs that share structural similarities, and act as inhibitors of HMG-CoA reductase.

What happens to cholesterol after synthesis?

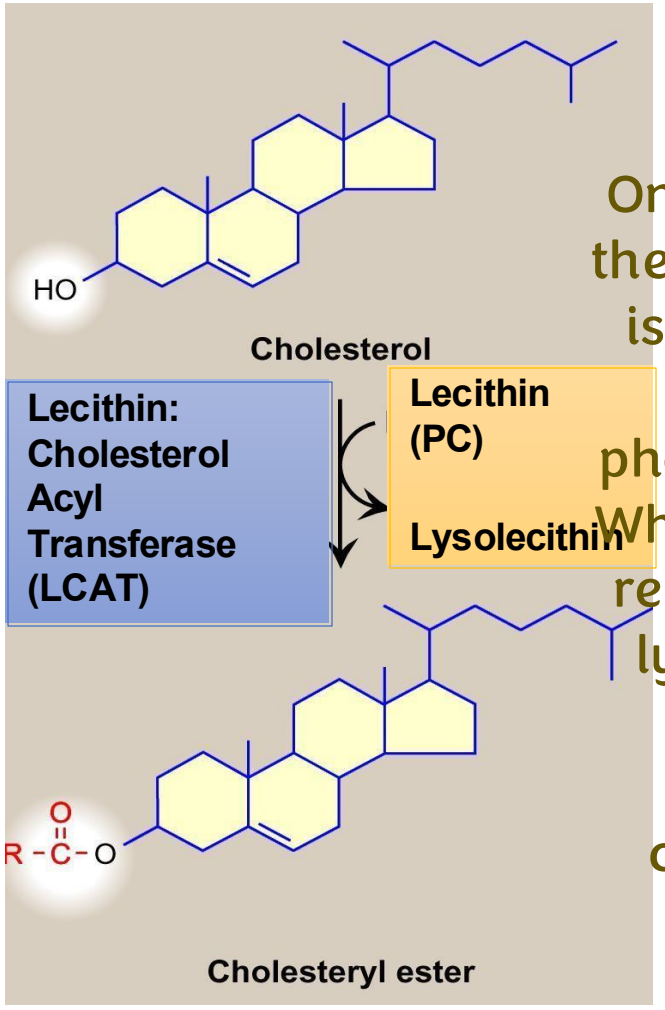
Esterification of Cholesterol

A large portion of cholesterol undergoes esterification to produce cholesterol ester.

Esterification of cholesterol inside the cell occurs using fatty acids in their active form, fatty acyl-CoA. The CoA group is removed, and esterification occurs with the hydroxyl group of cholesterol by the enzyme ACAT (Acyl- CoA cholesterol acyltransferase).



Esterification of cholesterol in the cells



Esterification of cholesterol in the plasma

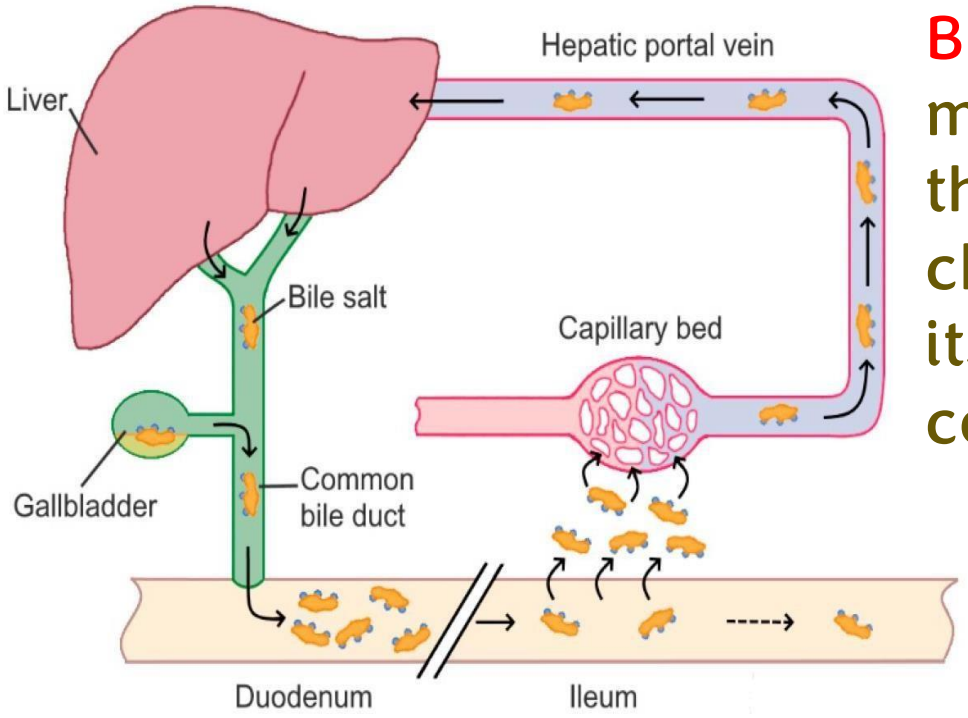
On the other hand, in the plasma, the source is different: lecithin (phospholipid phosphatidylcholine). When one fatty acid is removed, it becomes lysolecithin, which helps in the esterification of cholesterol by the enzyme LCAT.

Purpose of Cholesterol Esterification:

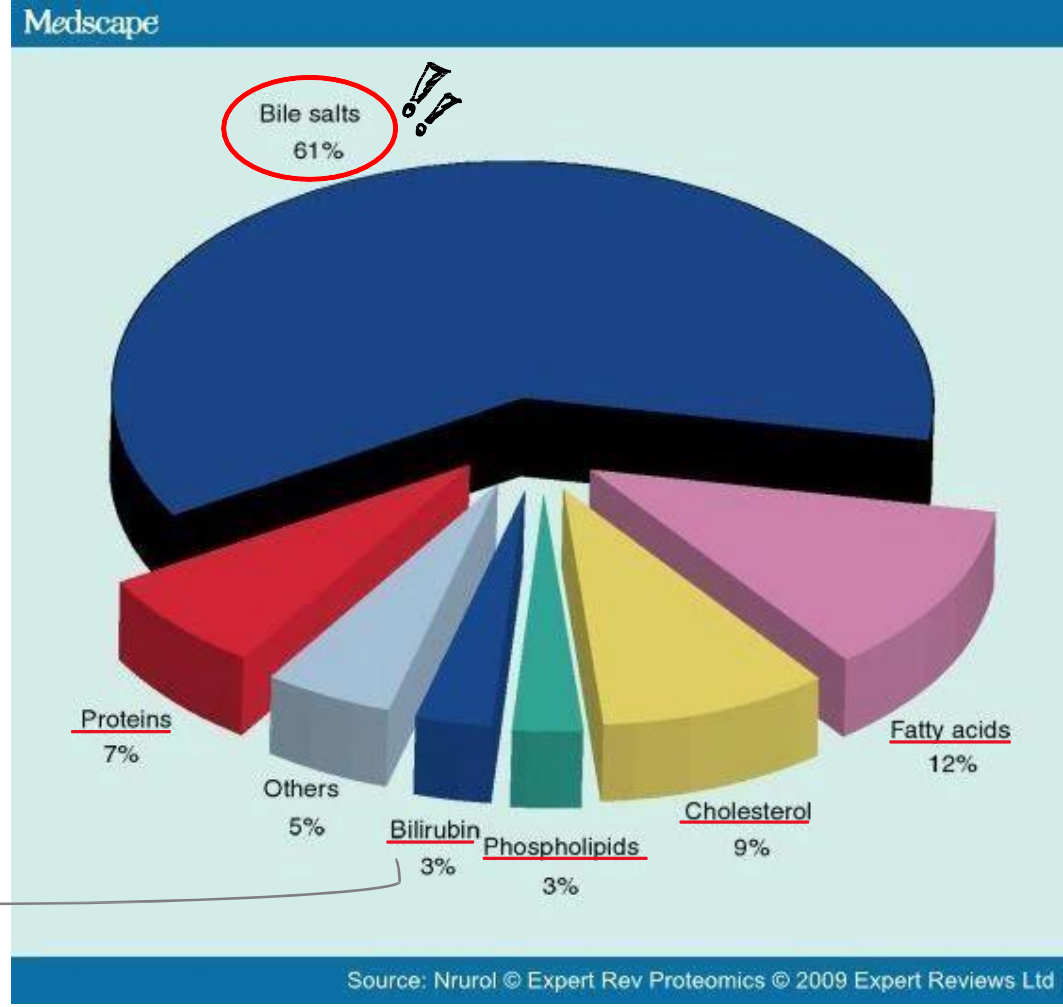
- Cholesterol esterification plays a crucial role in the synthesis of lipoproteins, especially HDL and LDL. Unlike other lipoproteins that primarily contain triglycerides (TAG), HDL and LDL are enriched with cholesterol. Initially, cholesterol enters these lipoproteins following its concentration gradient. However, as the process continues, it becomes energy- dependent, moving against the concentration gradient.The body maintains two separate concentration gradients: one for cholesterol and one for cholesterol esters. These molecules are distributed differently inside lipoproteins. Cholesterol, being amphipathic, has its hydrophilic hydroxyl group facing the outer layer of the lipoprotein, while the hydrophobic tail is oriented towards the inner core. On the other hand, cholesterol esters, which are hydrophobic, are located in the core of the lipoprotein particle. When cholesterol enters the cell, the fatty acid is released from the ester, allowing the cholesterol to be utilized in various cellular functions.

The use of cholesterol to make bile

- Bile consists of a **watery mixture** of organic and inorganic compounds.
  - PC and conjugated bile salts are the most important organic components of bile.



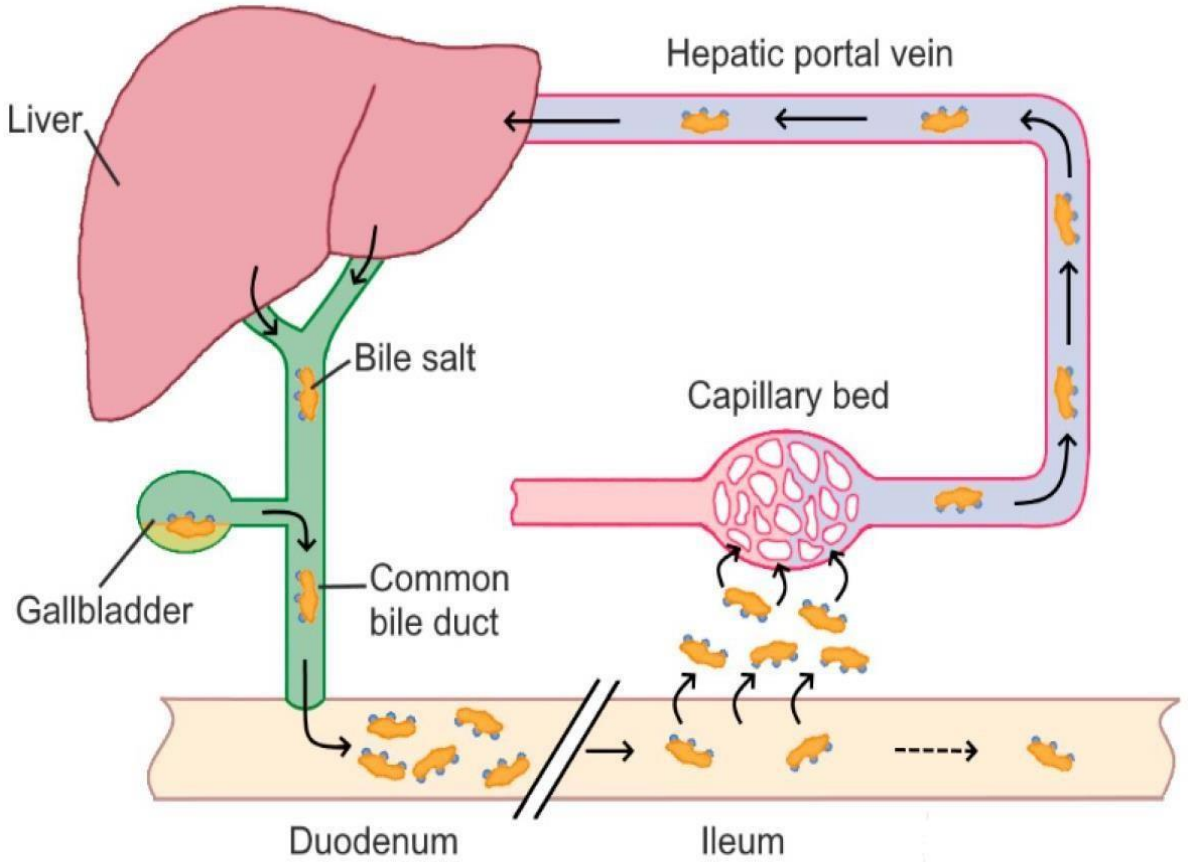
Bilirubin is a metabolite of the heme group, characterized by its yellowish color.



- Bile can either pass directly from the liver, where it is synthesized, into the duodenum through the common bile duct, or be stored in the gallbladder.

The use of cholesterol to make bile

- Hepatocytes synthesize bile, while the gallbladder stores bile acids and salts. When you eat food containing lipids, the stored bile is released all at once to perform its function.
- The common bile duct and pancreatic duct both empty into the duodenum, where bile secretion and lipase (which digests lipids) are released, respectively.



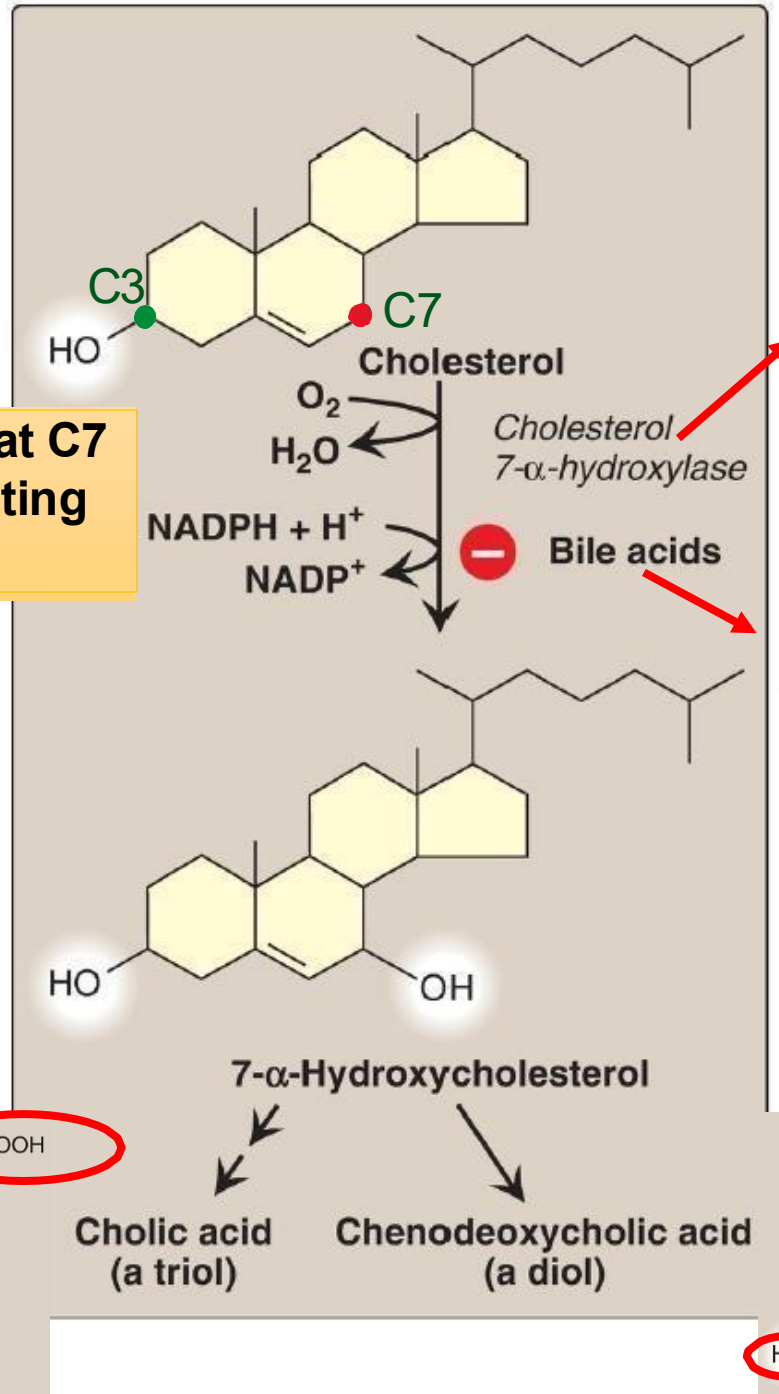
In urine tests , the color is an indication that something is wrong

When you eat a meal with high fat content you need more emulsifier
People who went through cholecystectomy cannot eat a meal with high fat content in one setting cause

The problem is loss of bile storage not loss of bile synthesis

Synthesis of Bile Acids and Salts

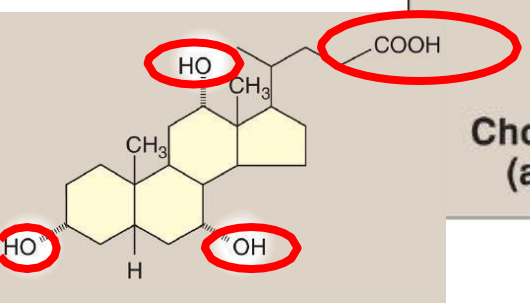
Hydroxylation at C7 is the rate-limiting Step

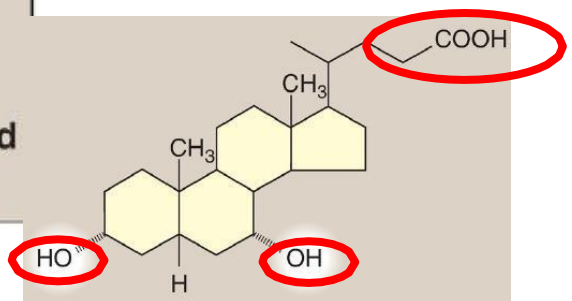


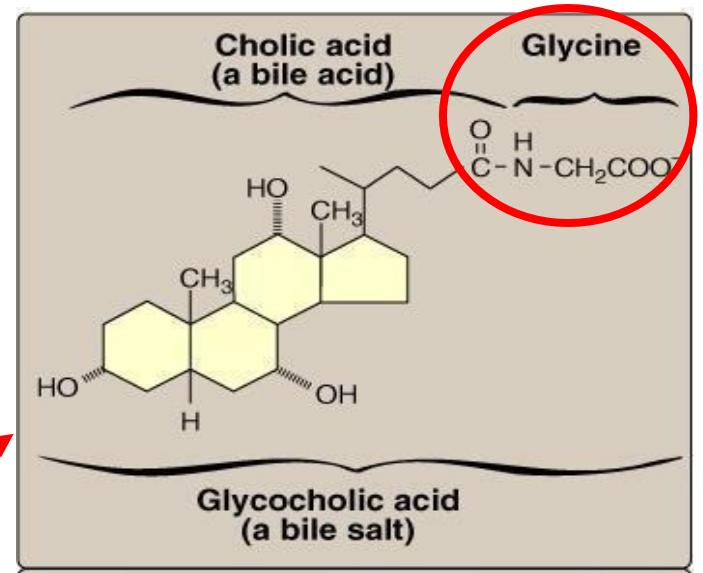
SER-associated cytochrome P450 monooxygenase found only in liver.

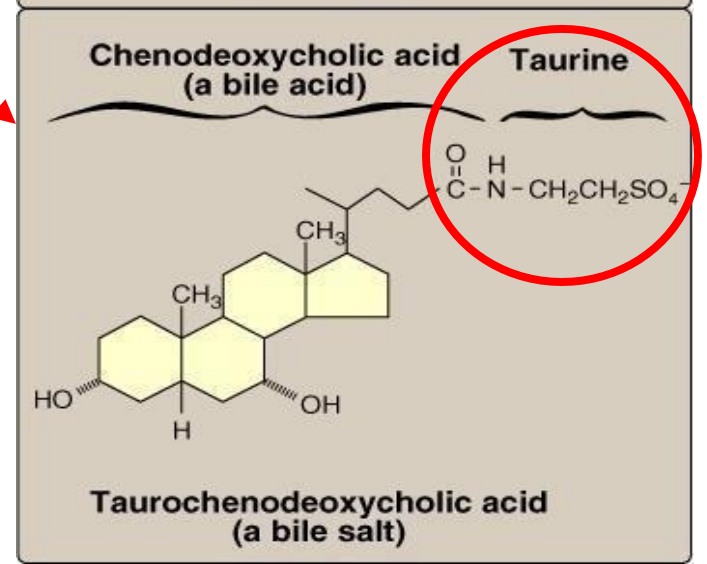
Inhibit the expression of cholesterol-7-hydroxylase

Conjugation





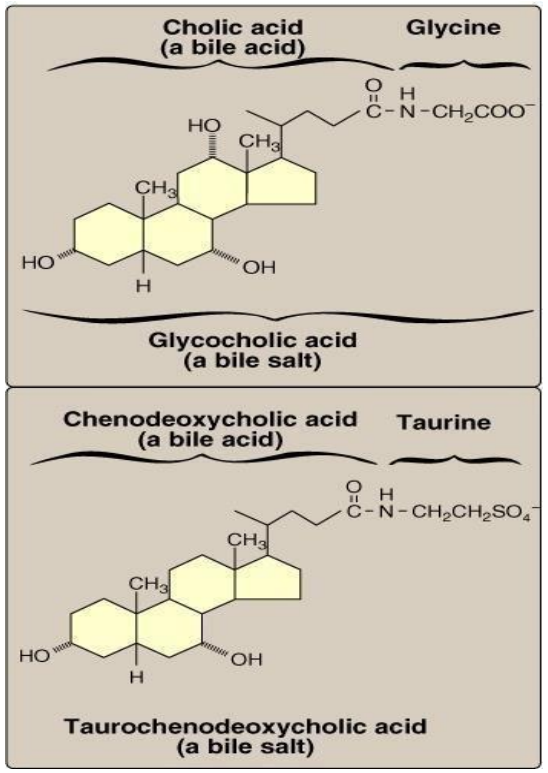




Synthesis of Bile Acids and Salts

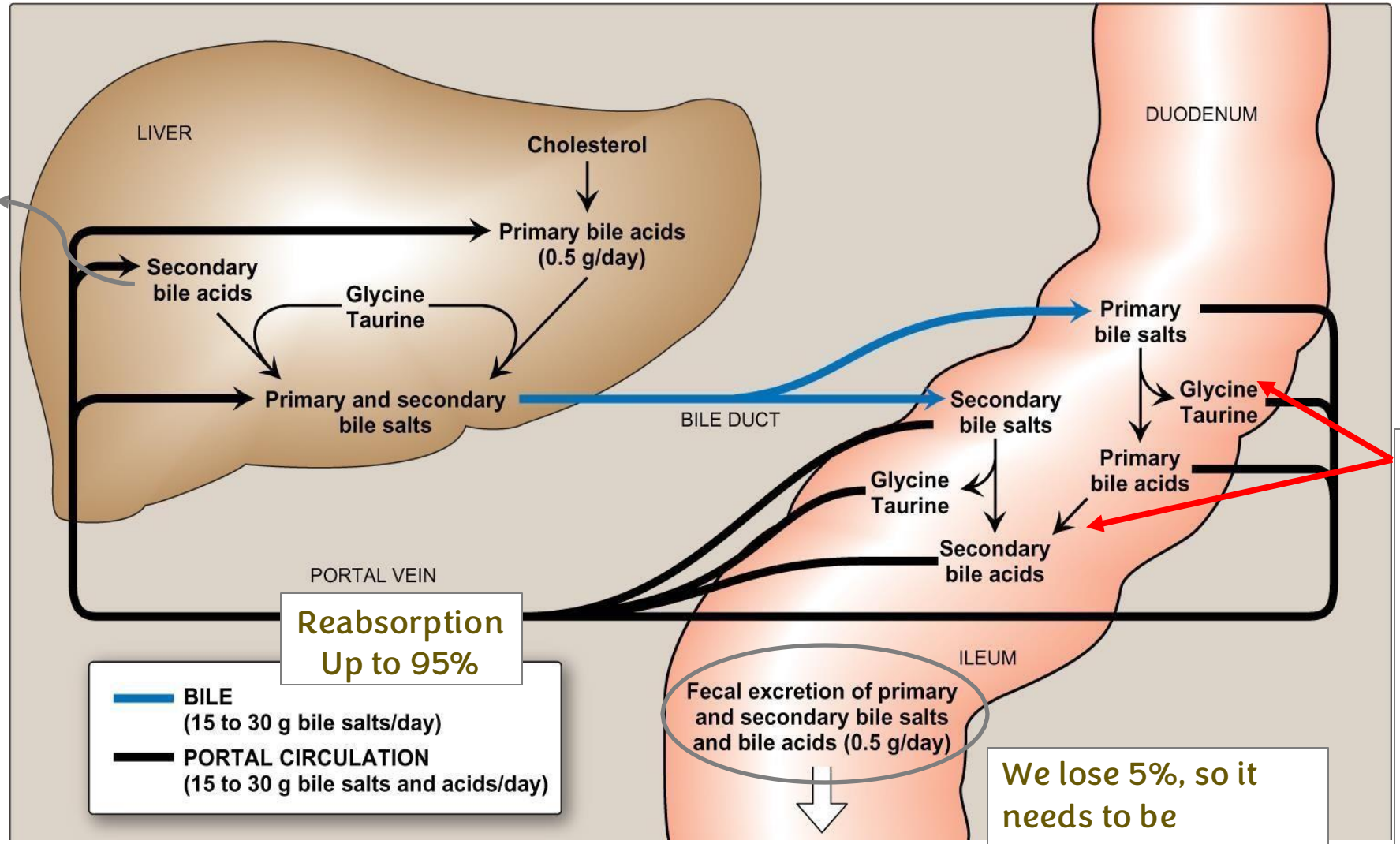
Go back to the recording for more understanding for this slide and the following one ☺

- Hydroxylation of cholesterol at carbon number 7 occurs via cholesterol 7-alpha hydroxylase, utilizing an oxygen molecule as part of a monooxygenase system (cytochrome P450). NADPH is oxidized, and the remaining oxygen atom is reduced to water. This step is the slowest and rate-limiting reaction in bile acid synthesis.
- The product, 7-hydroxycholesterol, can be used to synthesize different types of bile acids.
- A third hydroxyl group may be added, along with a carboxyl group at the side chain, forming cholic acid, which is considered a triol (with three hydroxyl groups).
- Chenodeoxycholic acid is formed when two hydroxyl groups (diol) and a carboxyl group are added to
- the side chain.
- These modifications of cholesterol increase its polarity,
- enhancing its binding to enzymes and facilitating digestion.
- Bile salts are produced when these bile acids interact with a base.
- In these two examples, the addition of a base increases the polarity of the molecule.
- Primary bile salts are produced directly.
- If a primary bile acid is conjugated with a base (glycine or taurine), it forms a primary bile salt. Secondary bile acids, after being modified, can also be conjugated with glycine or taurine to form secondary bile salts.



Enterohepatic circulation

It undergoes reabsorption and modification from the previous circulation.



We lose 5%, so it needs to be replenished.

Bacteria

Following their role in emulsification, primary bile salts are deconjugated by the intestinal normal flora which removes the base and converts them back into primary bile acids. Intestinal bacteria can further modify these primary bile acids into secondary bile acids.

Application: Cholelithiasis

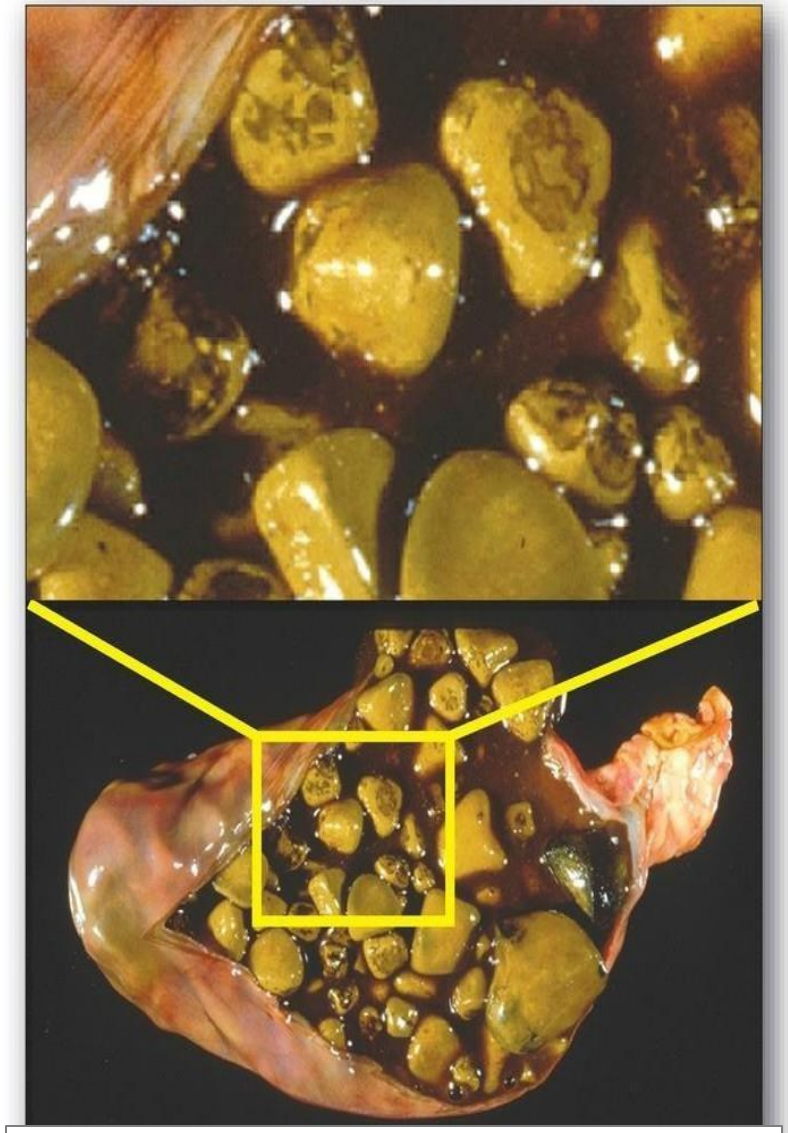
Bile Stone

- ↑Cholesterol or ↓bile acids → insolubility → gallbladder stones (cholelithiasis).

One hypothesis that explains cholelithiasis formation is oversaturation of bile, leading to cholesterol precipitation and the formation of a small nucleus that gradually grows into stones of various sizes and shapes. This can also occur if bile acid levels are low, causing cholesterol to accumulate.

In the gallbladder, the nucleus forms primarily from cholesterol and grows from it. In contrast, kidney stones can form from a variety of compounds, which serve as the nucleus for further growth.

- Treatment: <u>cholecystectomy</u> In severe cases.
  - Alternatively: oral administration of chenodeoxycholic acid results in a gradual (months to years) dissolution of the gallstones and reduces the effects of cholesterol oversaturation.



It may form in the gallbladder or bile duct, causing obstruction of the duct

Lowering Cholesterol Level

Conservative ways

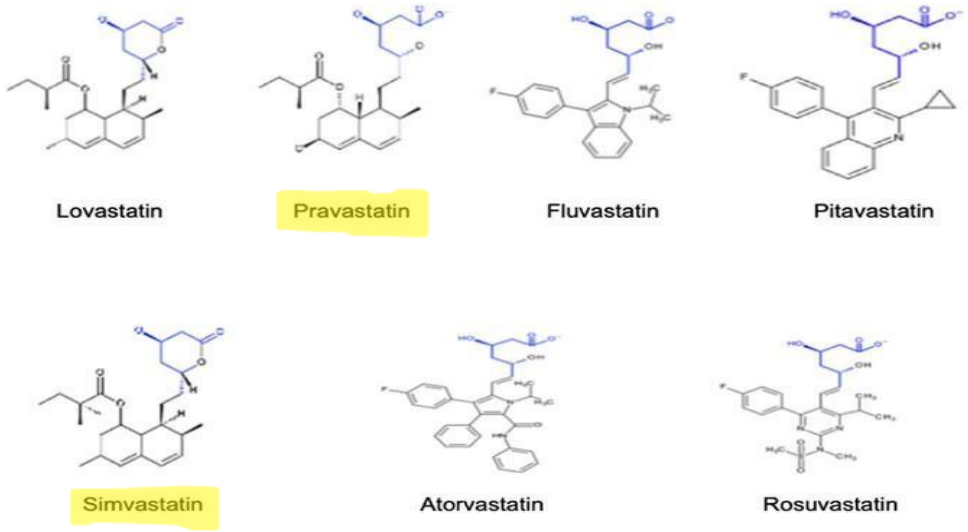
1. Dietary (Diet modification)

- ↓Cholesterol intake.
- ↑ PUSFA / SFA. increases the ratio of polyunsaturated fatty acids relative to saturated fatty acids, which reduces cholesterol absorption.
- ↑ Fiber. As it binds to cholesterol and facilitates its removal through feces.
- Ingestion of plant steroid esters. Because they reduce cholesterol absorption.

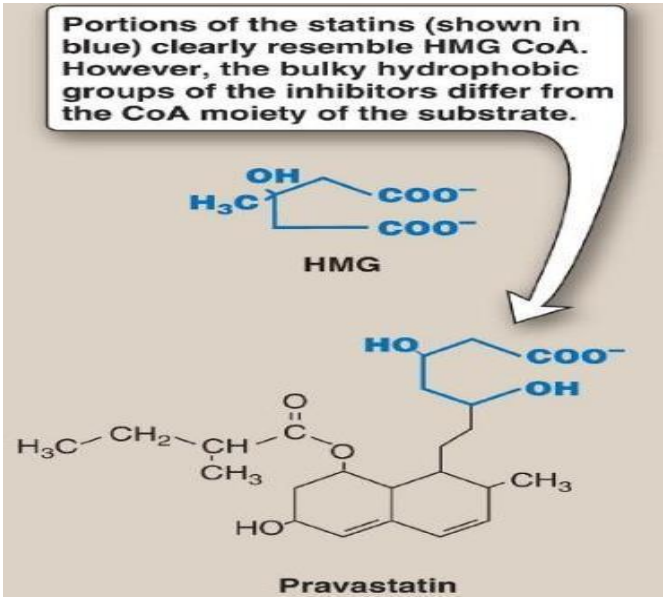
Lowering Cholesterol Level

2. Inhibition of Synthesis. Acts directly on the rate-limiting step

As mentioned earlier, HMG-CoA reductase is highly regulated to control cholesterol synthesis. Statins inhibit HMG-CoA reductase because their structure closely resembles the substrate.



Inhibitors of HMG CoA reductase (statins)



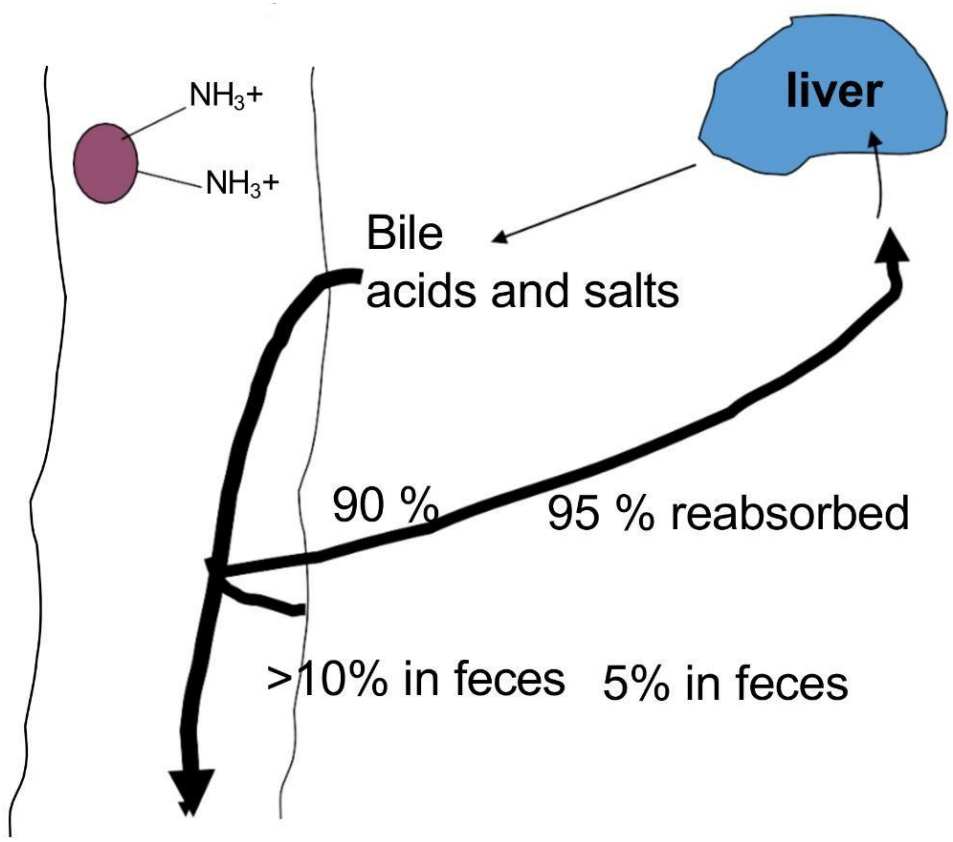
Lowering Cholesterol Level

3. Bile sequesterants such as <u>cholestyramine</u>

↓ Enterohepatic circulation of bile acids

- If we reduce reabsorption and increase excretion, the liver will use cholesterol to regenerate bile secretion.

- Bile sequestrants bind to bile acids and salts, reducing their reabsorption in the enterohepatic cycle, which leads to increased excretion.



Lipid-Soluble Vitamins

Vitamins

Are **organic** molecules required in **only trace amounts** that must be obtained through the diet because **our bodies do not have the ability to synthesize them.**

Vitamin classification

- Water-soluble and fat-soluble

Vitamin classification Water-soluble vitamins

- Found in the aqueous environment inside cells, where most of them are needed as components of coenzymes.
- B and C vitamins
- ¬OH, ¬COOH groups or other polar groups result in their water solubility
- Excreteted in Urine

Fat-soluble vitamins

- Stored in the body s fat deposits
- A, D, E, and K vitamins
- None has been identified as a coenzyme
- Accumulate in body fats so they have greater hazards of overdosing

Fat soluble vitamins can be found in adipose tissue.

Fat-soluble vitamins

TABLE 19.4 The Fat-Soluble Vitamins*

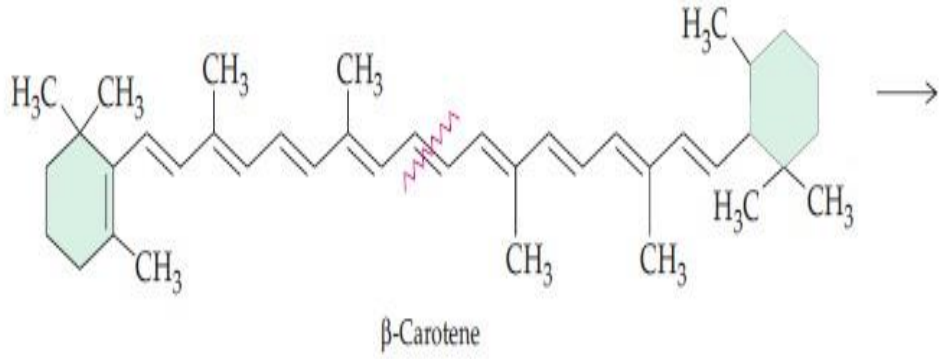
VITAMIN	SIGNIFICANCE	SOURCES	REFERENCE DAILY INTAKE**	EFFECTS OF DEFICIENCY	EFFECTS OF EXCESS
A	Maintains epithelia; required for synthesis of visual pigments; antioxidant	Leafy green and yellow vegetables	1000 μg	Retarded growth, night blindness, deterioration of epithelial membranes	Liver damage, skin peeling, central nervous system effects (nausea, anorexia)
D	Required for normal bone growth, calcium and phosphorus absorption at gut, and retention at kidneys	Synthesized in skin exposed to sunlight	10 μg	Rickets, skeletal deterioration	Calcium deposits in many tissues, disrupting functions
E	Prevents breakdown of vitamin A and fatty acids; antioxidant	Meat, milk, vegetables	10 mg	Anemia; other problems suspected	None reported
K	Essential for liver synthesis of prothrombin and other clotting factors	Vegetables; production by intestinal bacteria	80 μg	Bleeding disorders	Liver dysfunction, jaundice

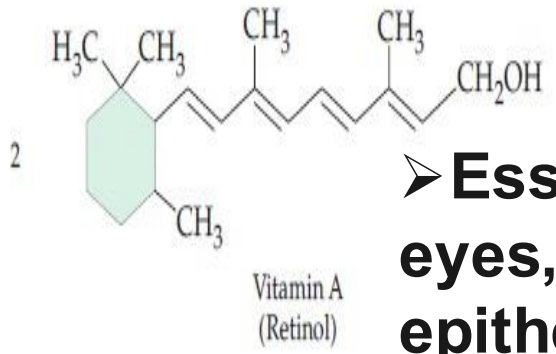
Vitamin k is needed for some post-transitional modifications.

*Adapted in part from Frederic H. Martini, Fundamentals of Anatomy and Physiology, 4th edition (Prentice Hall, 1998).

**RDI values are the basis for information on the Nutrition Facts Label included on most packaged foods. The values are based on the Recommended Dietary Allowances of 1968. RDIs for fat-soluble vitamins are often reported in International Units (IU), which are defined differently for each vitamin. The values given here are approximate equivalents in mass units.

Fat-soluble vitamins Vitamin A





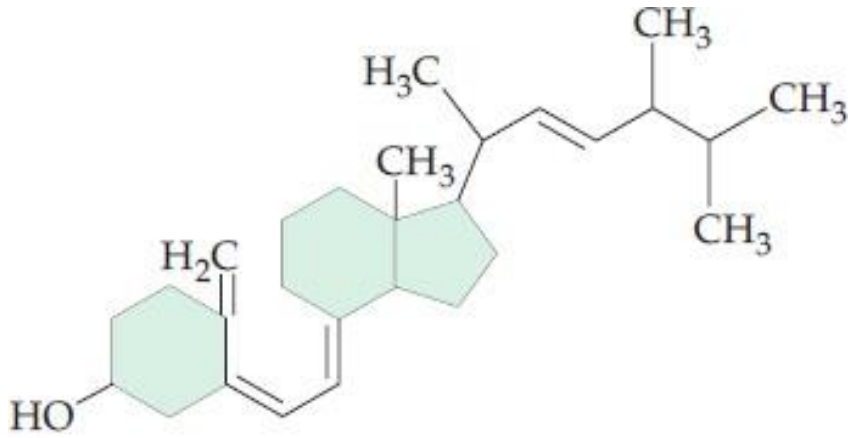
- **Essential for night vision, healthy eyes, and normal development of epithelial tissue.**
- **Has three active forms: retinol, retinal, and retinoic acid.**
- **Produced in the body by cleavage of β-carotene that gives an orange color to carrots and other vegetables**

Fat-soluble vitamins Vitamin D

- Related in structure to cholesterol
- Synthesized when UV light from the sun strikes a cholesterol derivative in the skin.
- In the kidney, vit. D is converted to a hormone that regulates Ca+2 **and phosphorus** absorption and bone formation.

It's synthesized first in the skin, and later on in the kidneys and liver.

Most people in the Middle East have vitamin D deficiency, even though they have good nutrition and adequate light exposure, this could be due to differences in the laboratory tests and the reference ranges applied

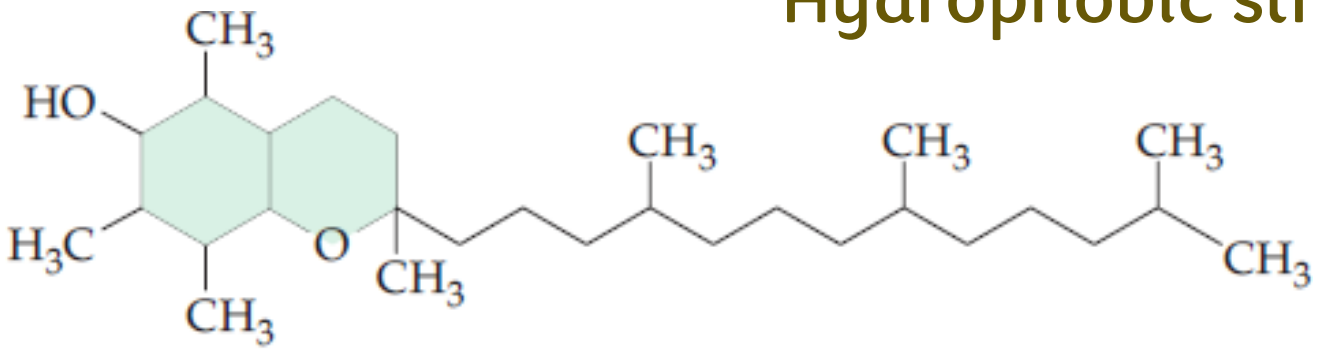


Vitamin D

Fat-soluble vitamins Vitamin E

- Comprises a group of structurally similar compounds called tocopherols, the most active of which is α-tocopherol
- Is an antioxidant
- It prevents the breakdown by oxidation of vitamin A and polyunsaturated fats.

Hydrophobic structure

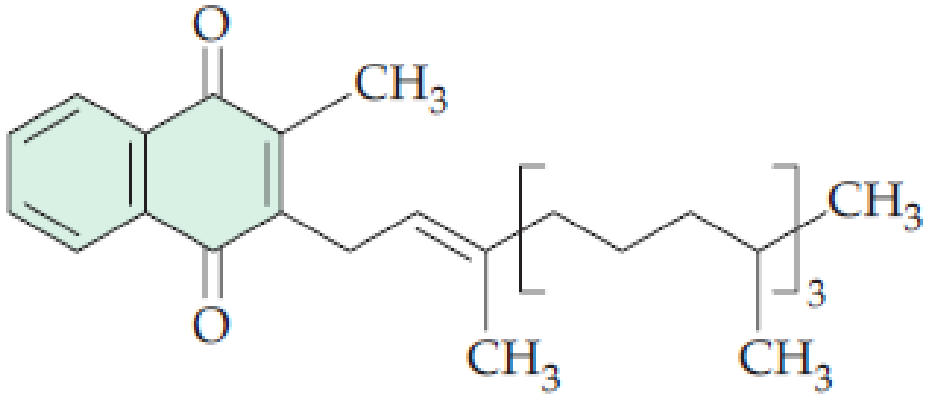


Vitamin E

Fat-soluble vitamins Vitamin K

It has many subtypes.

- Includes a number of structurally related compounds
- Hydrocarbon side chains of varying length.
- Synthesis of several blood-clotting factors.
- Produced by intestinal bacteria, so deficiencies are rare.



Vitamin K

Isoprenoid , in this specific subtype its repeated 3 times

رسالة من الفريق العلمي:

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide **4** , **5** , **23** Slide **10** (added)		Text added
V1 → V2			