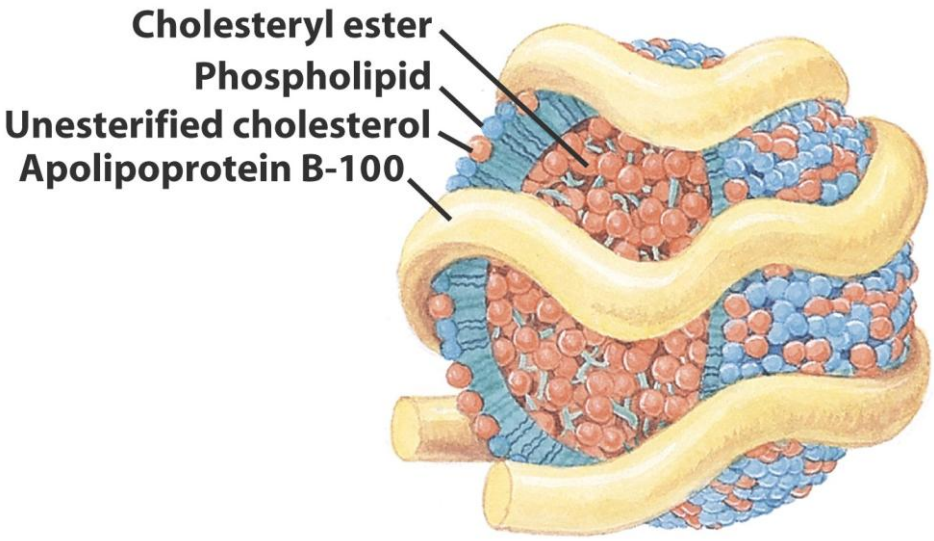
Lipid Metabolism

Digestion: A lingual lipase which secreted from the dorsal surface of the tongue, and the lipase secreted from stomach are not of much significance in humans compared to other animals. Most fat digestion, therefore, begins in the duodenum, where the ingested triglycerides are broken down into smaller chain fatty acids and monoglyceride molecules by pancreatic lipases enzymes after they are emulsified by bile salts(means break large fat droplets into smaller droplets).

Absorption: Absorption takes place through the mucosal lining of the small intestine, and when these products pass through the mucosa, they enter the mucosal cells (enterocytes). The fate of the fatty acids depends on their size. Fatty acids containing less than 10 to 12 carbon atoms are water-soluble enough that they pass through the enterocytes unmodified and are actively transported into the portal blood. They circulate as free fatty acids. The fatty acids containing more than 10 to 12 carbon atoms are too insoluble for this. They are resynthesis to triglycerides in the enterocytes. In addition, some of the absorbed cholesterol is esterified. The triglycerides and cholesterol esters are then coated with a layer of protein, cholesterol, and phospholipid to form chylomicrons. The chylomicrons enable fats and cholesterol to move within the aqueous environment of your lymphatic and circulatory systems. Chylomicrons leave the enterocytes and enter the lymphatic system via lacteals in the villi of the intestine because they are too large to pass through the junctions between capillary endothelial cells. From the lymphatic system, the chylomicrons are transported to the circulatory system.



The chylomicrons

Transport: lipids are transported as a variety of lipoproteins, packages which contain fat, proteins, phospholipids and cholesterol in varying proportions.

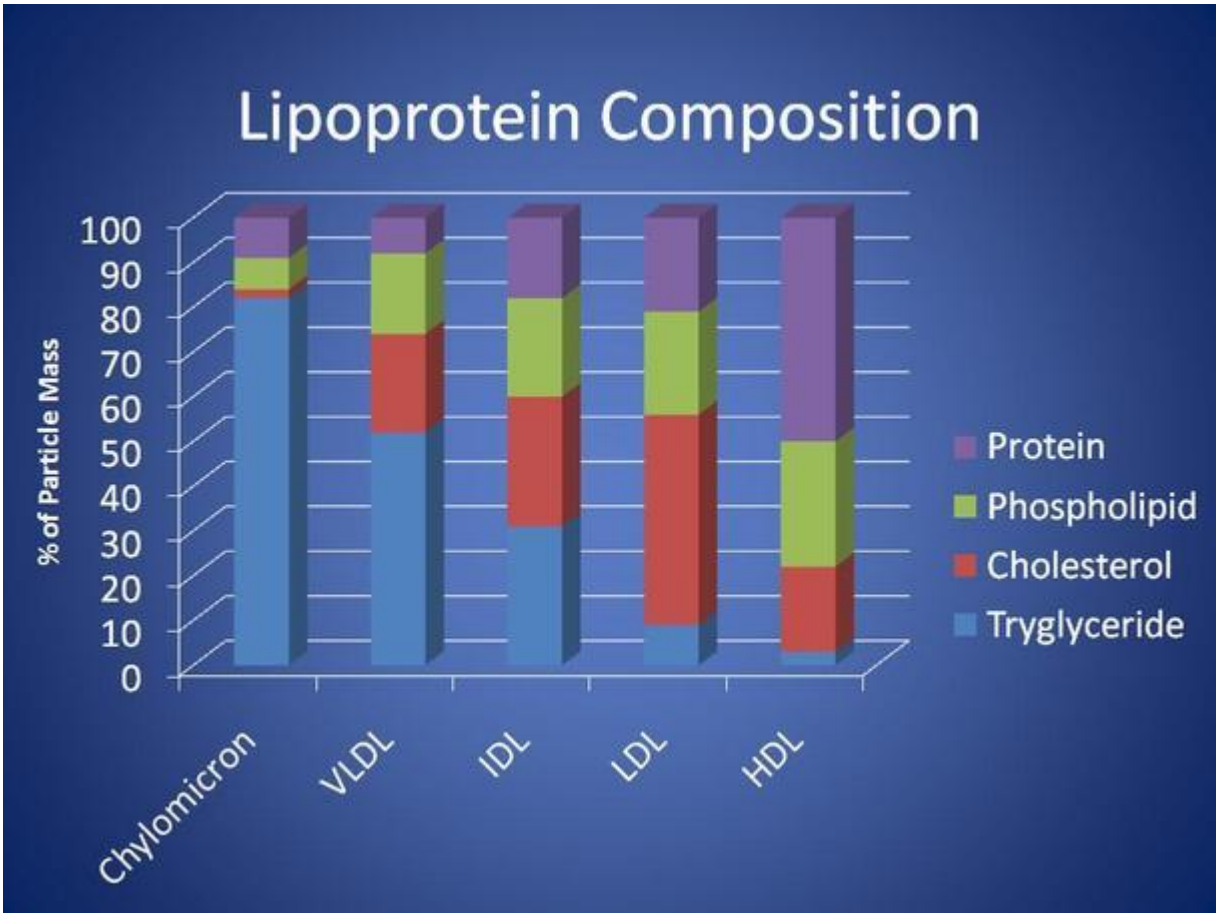
Main types of lipoproteins

1- Chylomicrons: are formed in intestine mucous.

2- VLDLs: very low density lipoproteins, created in liver.

3- LDLs: low density lipoproteins. Created in blood as cells remove triglycerides. These contain what the medical community refers to as “bad cholesterol”. LDLs travel to the peripheral circulation and contribute to atherosclerosis, the formation of fatty plaques in arteries.

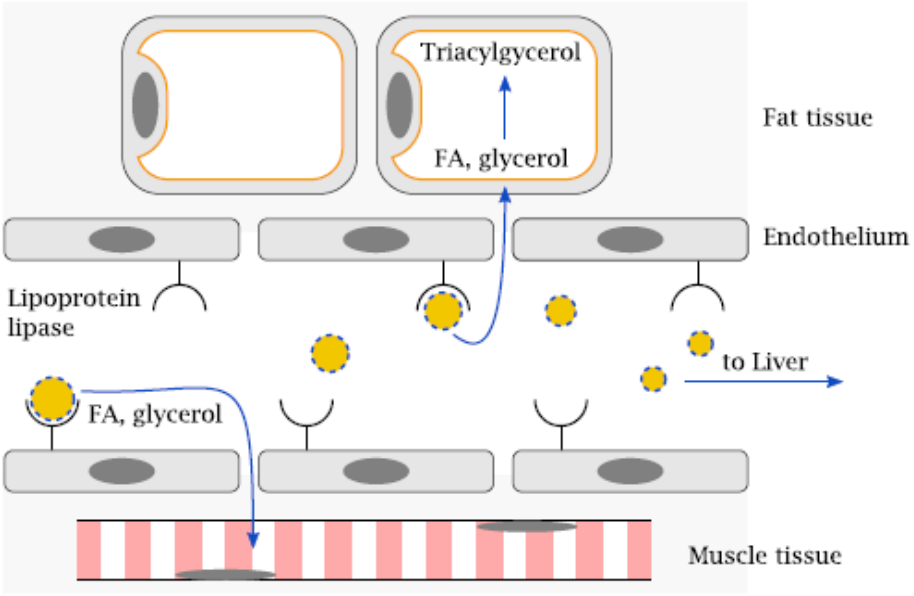
4- HDLs: high density lipoproteins. Made in liver for return of cholesterol there. Contain “good cholesterol”. HDLs travel to the liver where their components are processed into useful body chemicals.



Lipoproteins content

Once the chylomicrons have entered the circulation, the capillary wall barrier must again be overcome in the delivery of triacylglycerol (triglyceride) to extravascular cells. This is accomplished with the help of lipoprotein lipase, which is located on the endothelial surface. It binds the chylomicrons and extracts triacylglycerol from them, which it then cleaves again to fatty acids and glycerol. These small molecules can cross the endothelial barrier by diffusion and reach the cells in the surrounding tissue. In adipose cells, the fatty acids are combined with glycerol yet again for storage. In other cell types, most notably muscle cells, they may either be stored or degraded directly to acetyl-CoA, which is then consumed in the TCA cycle and the respiratory chain. The remnants of chylomicrons, depleted of most of their triacylglycerol, are captured by the liver and degraded. The cholesterol and remaining fat released in the process is either utilized in the liver or repackaged into other

lipoprotein particles.



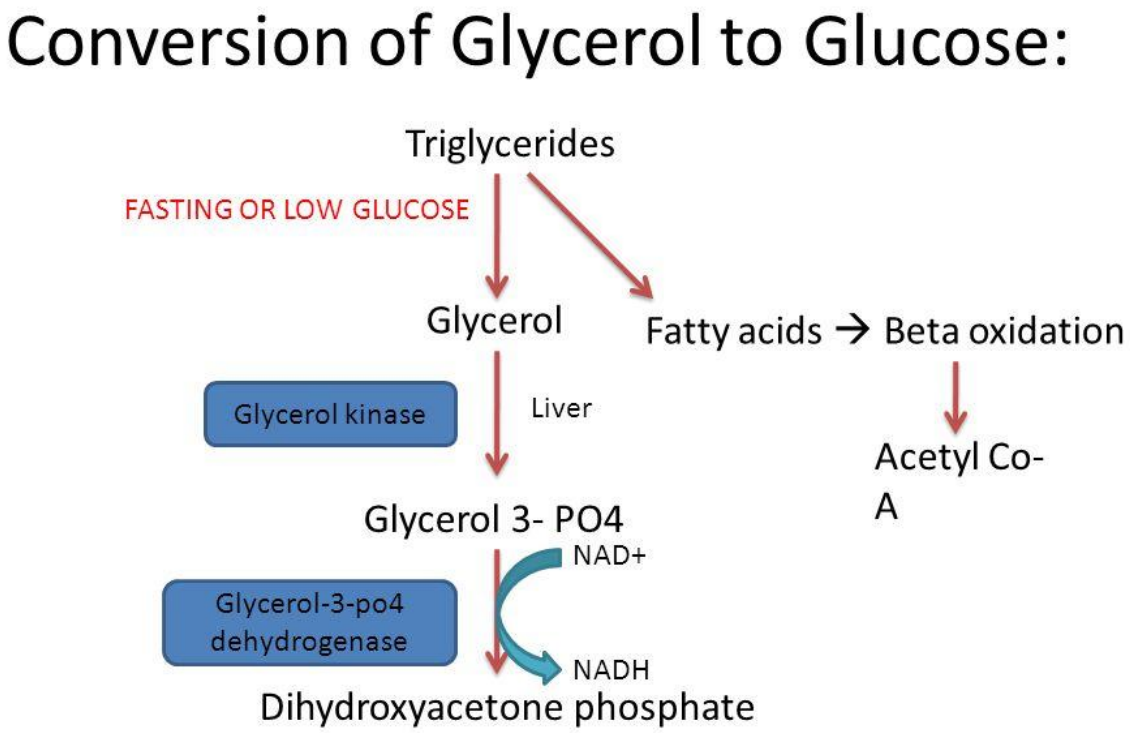
Lipid metabolism

Triglyceride metabolism

To obtain energy from fat, triglycerides must first be broken down by hydrolysis into their two principal components, fatty acids and glycerol. This process, called lipolysis, takes place in the cytoplasm.

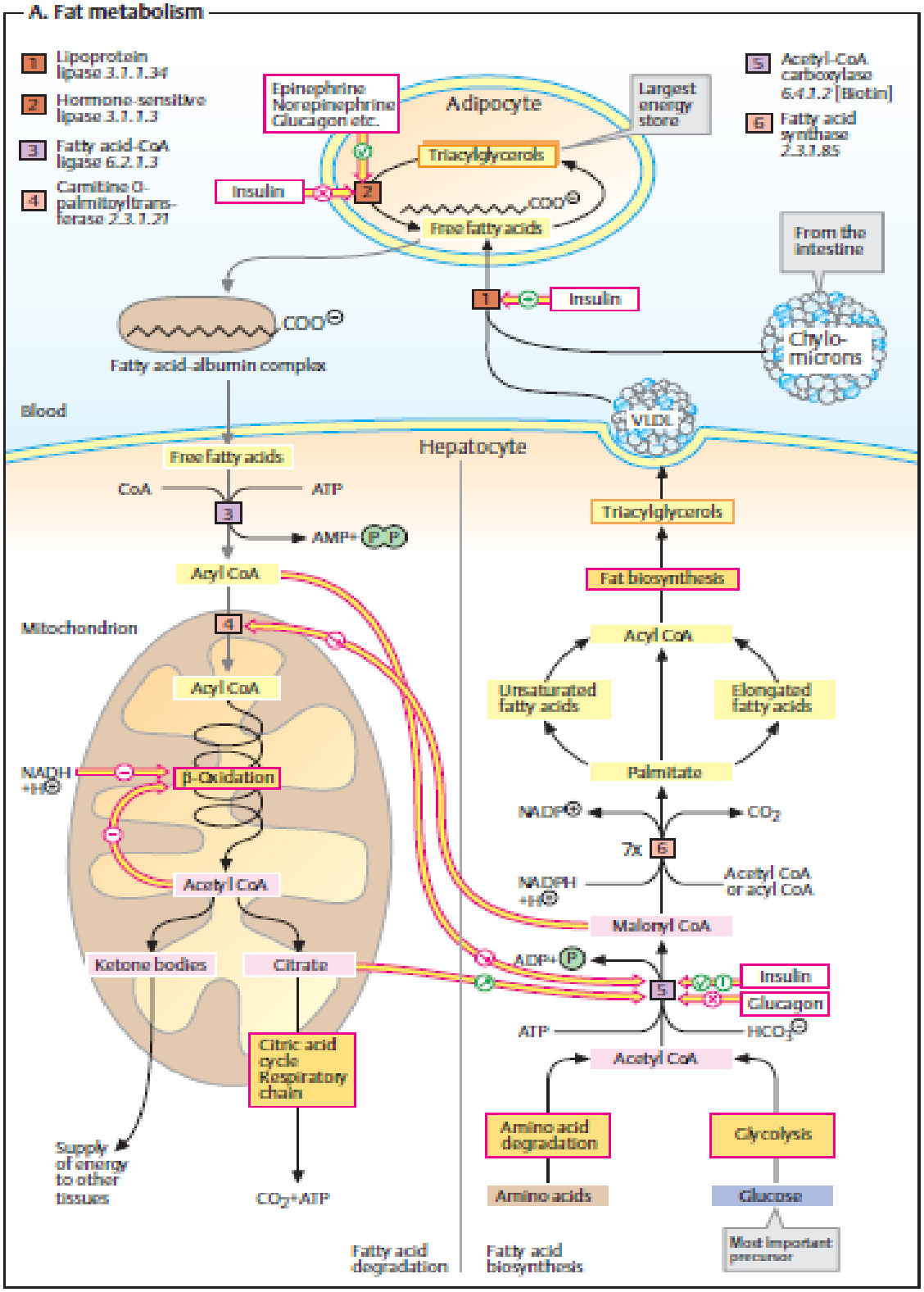
A-Fate of glycerol:

The glycerol that is released from triglycerides after lipolysis can enter the glycolysis pathway directly in liver and kidney, but not in adipose tissue due to the present of glycerokinase enzyme in liver and kidney and, thus, provide energy for cellular metabolism or it can be converted to glucose through gluconeogenesis.



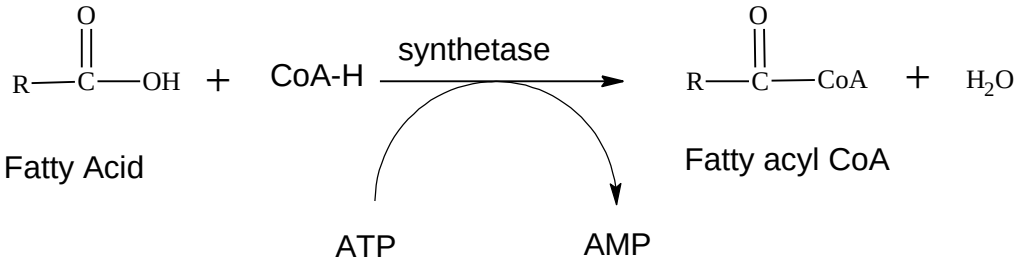
B-Fate of fatty acid:

The breakdown of fatty acids, called **fatty acid oxidation** , begins in the cytoplasm, where fatty acids are converted into fatty acyl CoA molecules. This fatty acyl CoA combines with carnitine to create a fatty acyl carnitine molecule, which helps to transport the fatty acid across the mitochondrial membrane. Once inside the mitochondrial matrix, the fatty acyl carnitine molecule is converted back into fatty acyl CoA and then into acetyl CoA. The newly formed acetyl CoA enters the Krebs cycle and is used to produce ATP in the same way as acetyl CoA derived from pyruvate.

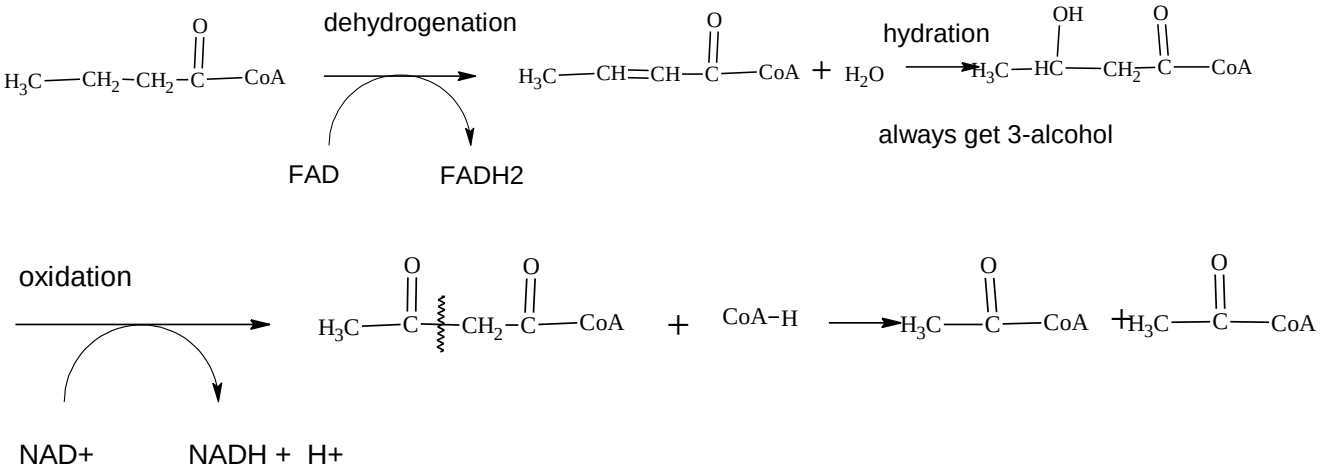

A. Fat metabolism
1 Lipoprotein lipase 3.1.1.34
2 Hormone-sensitive lipase 3.1.1.3
3 Fatty acid-CoA ligase 6.2.1.3
4 Carnitine O-palmitoyltrans-ferase 2.3.1.21
5 Acetyl-CoA carboxylase 6.4.1.2 [Biotin]
6 Fatty acid synthase 2.3.1.85
Epinephrine Norepinephrine Glucagon etc.
Adipocyte
Largest energy store
Triacylglycerols
Insulin
Free fatty acids
From the intestine
Insulin
Chylo-microns
Fatty acid-albumin complex
Blood
VLDL
Hepatocyte
Free fatty acids
CoA
ATP
AMP+
Acyl CoA
Triacylglycerols
Fat biosynthesis
Mitochondrion
Acyl CoA
Unsaturated fatty acids
Elongated fatty acids
NADH +H
β-Oxidation
Palmitate
NADP
CO2
7x
Acetyl CoA
Acetyl CoA or acyl CoA
NADPH +H
Malonyl CoA
Ketone bodies
Citrate
ADP+
Insulin
Glucagon
ATP
HCO3
Citric acid cycle Respiratory chain
Acetyl CoA
Amino acid degradation
Glycolysis
Supply of energy to other tissues
CO2+ATP
Amino acids
Glucose
Most important precursor
Fatty acid degradation
Fatty acid biosynthesis

I. Step One

- Fatty acid must be activated to fatty acyl CoA (- 2 ATP)



II. Step Two



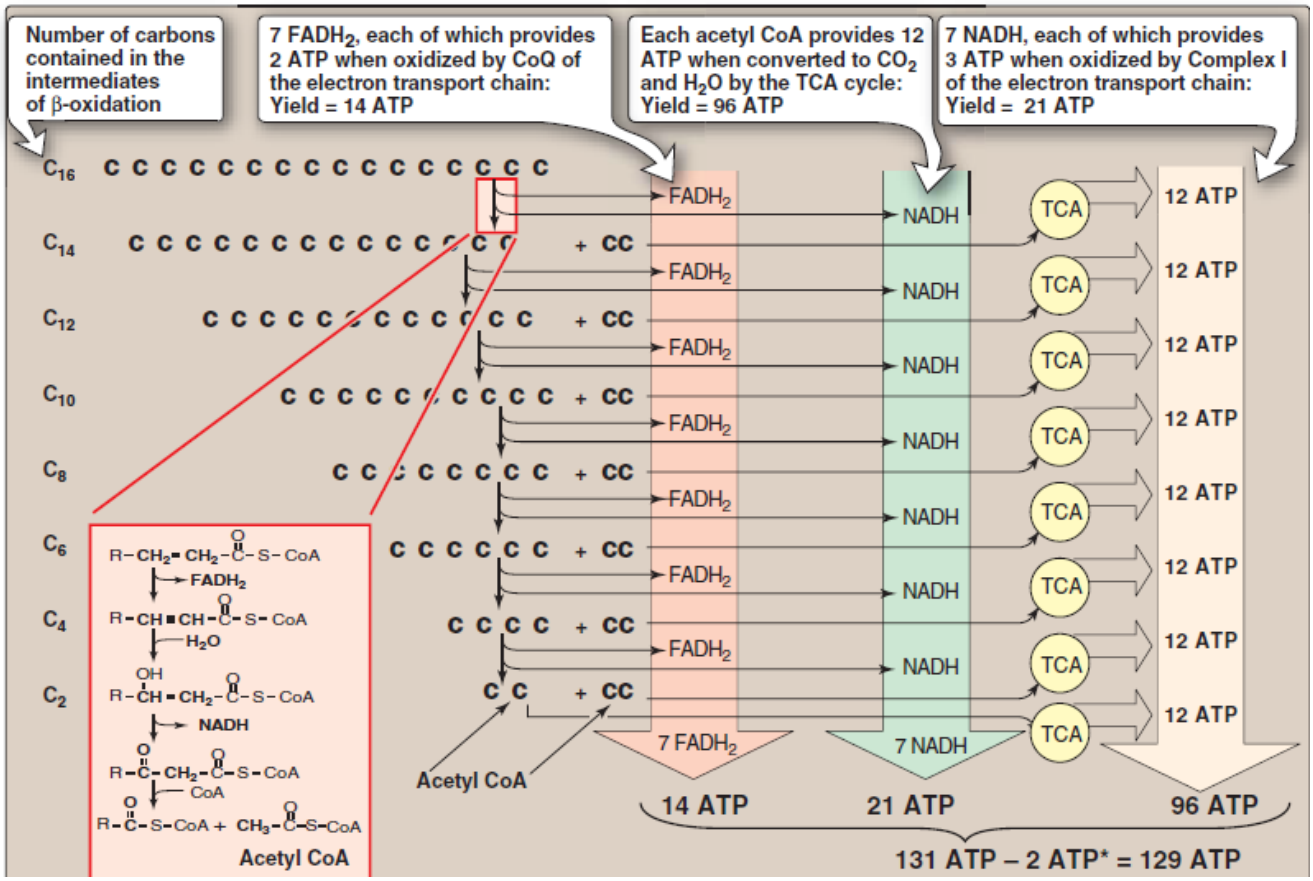
So: If I have a fatty acid which is 16 carbons long, I will end up with 16/2 = 8 acetyl CoA molecules, 7 $FADH_2$'s and 7 NADH's

- The Fate of acetyl CoA is

1) Enter Krebs cycle.

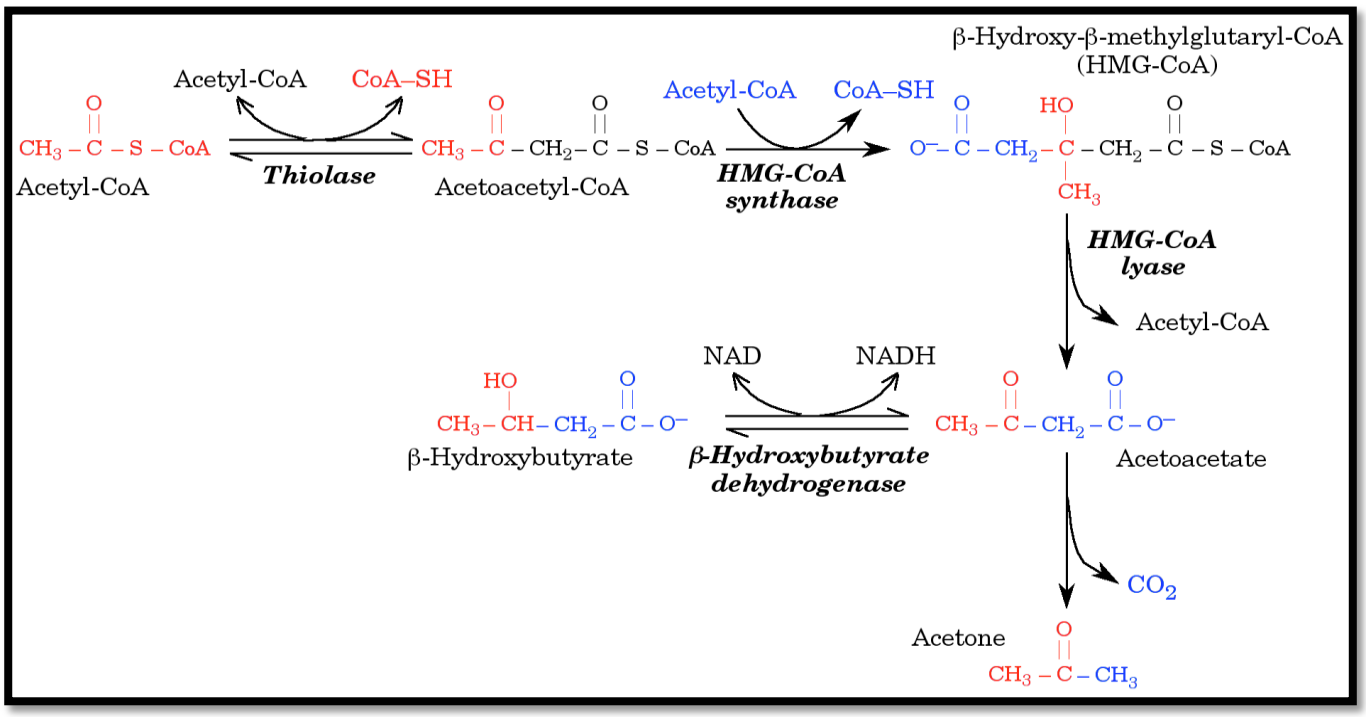
2) Formation of ketone bodies (ketogenesis).

3) Used to reform fatty acids

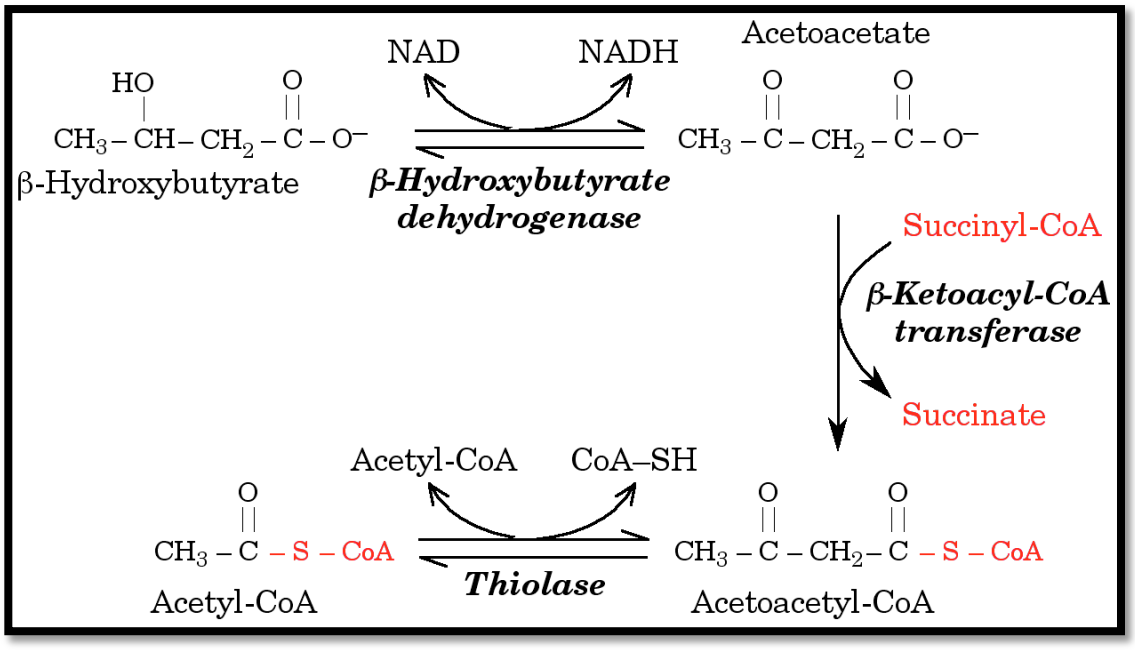


Ketogenesis

Ketone bodies are acetoacetate, acetone, and β-hydroxybutyrate. Ketone bodies are synthesized from acetyl-CoA (oxidation of fatty acids and glucose) in liver mitochondria. These ketone bodies can serve as a fuel source if glucose levels are too low in the body. Breakdown of ketone bodies in the brain, muscle and other tissues to acetyl-CoA, which oxidize in the Krebs cycle to give energy, H_2O and CO_2 is called ketolysis .



Ketogenesis



Ketolysis

Cholesterol metabolism

Biological significance of cholesterol:

1. Cholesterol is an essential lipid constituent of cell membranes
2. Cholesterol is a precursor of steroid hormones and of bile acids
3. Intermediates of cholesterol biosynthesis are required to make vitamin D
4. High plasma cholesterol promotes atherosclerosis

Cholesterol synthesis

Cholesterol synthesis starts with acetyl-CoA, which is used to synthesize hydroxymethylglutaryl- CoA (HMG-CoA). All steps downstream of HMG-CoA occur in the smooth endoplasmic reticulum. HMG-CoA reductase reduces HMG-CoA to mevalonate. Mevalonate is converted to various isoprene intermediates that converted to squalene. Squalene is converted lanosterol that converted to cholesterol.