Chapter 2
Lipid metabolism

●**Lipids** = acylglycerols (glycerol+fatty acids)

●**Acylglycerols** constitute the majority of lipids in the body, and **triacylglycerol** is the major type in fat deposits in our body, and in food

Triacylglycerol= 3 fatty acids+glycerol

●They are **hydrophobic molecules** (insoluble in water) and must be hydrolyzed (يتكسر) and emulsified (يستحلب) to very small droplets (called micelles) before they can be absorbed in the body

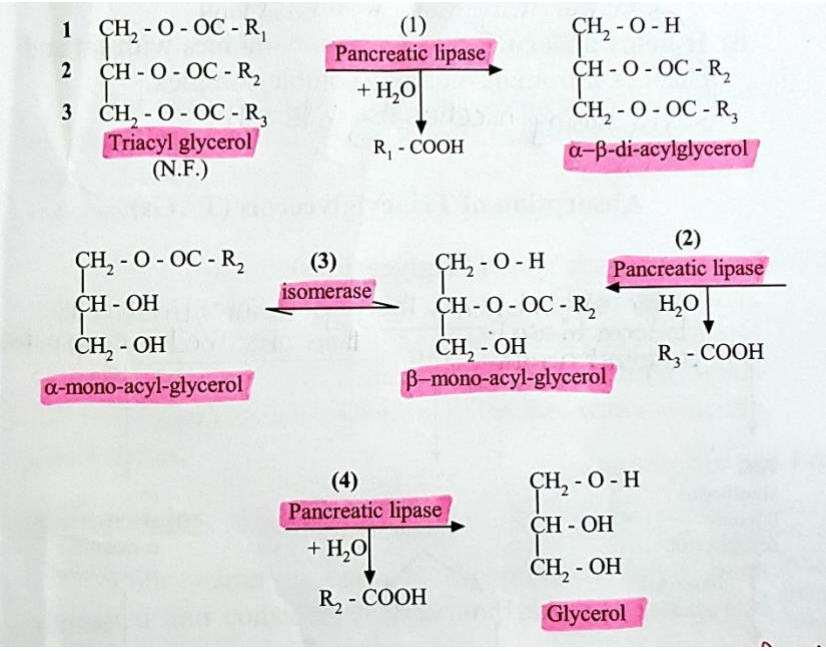
Digestion of lipids:

Lingual lipase: it is present **in the oral cavity** and it's the first enzyme to act on but still it's very weak

Pancreatic lipase:

● it's the **most important enzyme** in lipid digestion, It's secreted into the **small intestine** (its digestion takes place in small intestine) and needs a special pancreatic protein for its activity, this protein is called colipase

●It is specific for the primary ester links (addition of OH group to primary carbons) i.e positions **1 and 3 triacylglycelors** as follows:



●Pancreatic lipase or colipase deficiency will lead to lipid **malabsorption** عدم امتصاص الدهون المهضومة

Steatorrhea; it's a clinical condition characterized by excretion of fat in stools **due to malabsorption and indigestion** عدم هضم,the stools become whitish and watery, **it leads to dehydration and anemia**

Activators of pancreatic lipase:

1-Calcium

2-bile salts (secreted from the liver when lipids reach the duodenum)

Functions of bile salts:

1-helps in digestion of fats as:

a) It causes emulsification of fats (breakage into small Particles) and lowering the surface tension, so the surface area upon which the enzyme acts increases

هيخلي المساحه اللي بيشتغل عليها الانزيم تزيد

b) It activates the pancreatic lipase which will hydrolyze triacylglycerol into **monoacylglyceryol + fatty acid + glycerol**

2- it helps in absorption of fats as it combines with fat and changes it from insoluble to soluble complex **(by forming micelles)**

لازم يبقى لازم يبقى soluble علشان ما يرجعوش الجليسرول والfatty acids يمسكوا في بعض ثاني ويبقى زي نقطه زيت بتكبر و يسد الشرايين

Lipid transport and storage:

●fat absorbed from the diet, and lipid synthesized by the liver and adipose tissue must be transported between tissues and organs **for utilisation and storage**

●Since lipids are **insoluble** in water and the blood plasma **is aqueous**, so lipoproteins are formed **to transport lipids in plasma**, as lipoprotiens are water-miscible

●Lipoproteins are composed of **proteins + lipids**, proteins are water soluble (hydrophilic) and **form the outer membrane together with amphipathic lipids**

amphipathic lipids means lipids that can be both hydrophobic and hydrophilic and these amphipathic lipids are phospholipids and cholesterol

●So the lipoproteins is formed of outer hydrophilic soluble layer which is **composed of proteins + phospholipids and cholesterol**, and the inner hydrophobic layer is formed of **triacylglycerol and cholesterol esters**

For illustration:

After absorption of glycerol and fatty acids, they diffuse inside the intestinal cells to **reform tryiacylglycerol again**, then become absorbed inside the lymphatics and systemic circulation to reach extrahepatic tissue (any tissue outside the liver), then they move to the liver and **re-secreted in EHT,** also adipose tissue secretes lipids in the circulation and continue the same cycle **(circulation and EHT then liver then EHT again then liver and so on)**

Lipoprotiens:

●They can be separated by electrophoresis into **alpha**, **beta** and **pre-beta lipoproteins** ,and they are separated according to their **charges** and **molecular weight**

And also separated by ultracentrifugation according to their **densities**

●The protein part of lipoproteins is called **apolipoprotein (Apo)**

Types of lipoproteins

1-chylomicrons:

●Its mainprotein part is called Apo-B-48

●Its pathway:

1)Formed in small intestine

2)then diffuse to lymphatics

3)then go to the circulation

4)then to the EHT (not liver), and there they find **lipoprotein lipase** enzyme which **hydrolyses TAG** inside chylomicrons **into glycerol+fatty acids** ,and these smaller particles are called chylomicron remnants

5)these remnants will be absorbed in the liver

كده للدهون اللي رايحه للكبد هتبقى كثيره في هتعمل مرض اسمه fatty liverعشان كده هيحصل الخطوه اللي جاية

6)the liver forms Apo-B-100 from these remnants which will enter in the second lipoprotein **"VLDL"**

في الخطوه الرابعه الchylomicrons تاخذ Apo-C2 and Apo E منHDL عشان تشغل ال lipoprotein lipase و الخطوة دي بيعملها ال VLDL بردو

●**It's rich in TAG**

2-Very low density lipoproteins (VLDL or pre-beta lipoproteins):

●**They are derived from the liver**

●**Its main protein part is called apo-B 100**

●**it's rich in triacylglycerol**

●it transports **triacylglycerol from liver to peripheral tissues**

●It's metabolism forms low-density lipoproteins

ما بين VLDL and LDL في خطوه في النص intermediate اسمها IDL

3-low density lipoprotein (LDL or Beta lipoproteins):

●**It represents a final stage in the catabolism of VLDL**

●**Its main protein part is called apo-B 100**

●**It's rich in cholesterol**

●it transports **cholesterol from liver to peripheral tissues**

كثافتها قليله لان فيها بروتينات وphospholipids قليله اللي هما اصلا كثافتهم عاليا، وفي نفس الوقت فيها كميه كبيره من ال triacylglycerol و الكوليسترول اللي هم كثافتهم قليله، عشان كده لو وكميتها زادت في الدم بتبقى مشكله لان فيها دهون كثيره تعمل امراض في القلب و تصلب الشرايين

●The level of LDL in blood is related to the incidence of cardiovascular diseases such as **atherosclerosis, myocardial infarction and thrombosis**

●LDL receptors are present in all cells but **more abundant in liver and adrenal Cortex** and the Binding of LDL to its receptor needs apo B100 (the outer surface protein part of this lipoprotein)

●It has step growth (بتكمل خطوات شغلها) **in the liver or EHT**

4-High density lipoproteins (HDL or alpha-lipoproteins):

●**Its main protein part is Apo A**

●**It's functions:**

a) involved in VLDL and chylomicrons metabolism

b) reverse cholesterol transport, it's the main transport form of cholesterol **from peripheral tissues to the liver** to be excreted through the bile (the opposite of LDL)

●reverse cholesterol transport is **helped by LCAT enzyme**

●HDL is preferred in our body than LDL, as it is protective for our body because it contains large amount of proteins and phospholipids and small amounts of Triacylglycerol and cholesterol (The opposite if LDL)

Types of apolipoproteins:

1-Apolipoprotein A:

They include Apo-A-1, Apo-A-2, Apo-A-4 and Apo-A-5

a) 1 and 4 are structural activators of LCAT enzyme
b) 2 is structural inhibited of hepatic lipase
c) They are the major proteins of HDL
d) They are synthesized in liver and small intestine

2-Apolipoprotein B:

They include:

a) **Apo-B-48** of chylomicrons which is synthesized in the intestine (48 means that only 48% of amino acids are used in protein synthesis)
b) **Apo-B-100** of LDL and VLDL which is synthesized in the liver (100 means that all A.A are used)

مكتوب في الكتاب انها في الHDL كمان بس دكتور خورج قال انها غلط

3-Apolipoprotein C:

They include Apo-C-1, Apo-C-2 and Apo-C-3

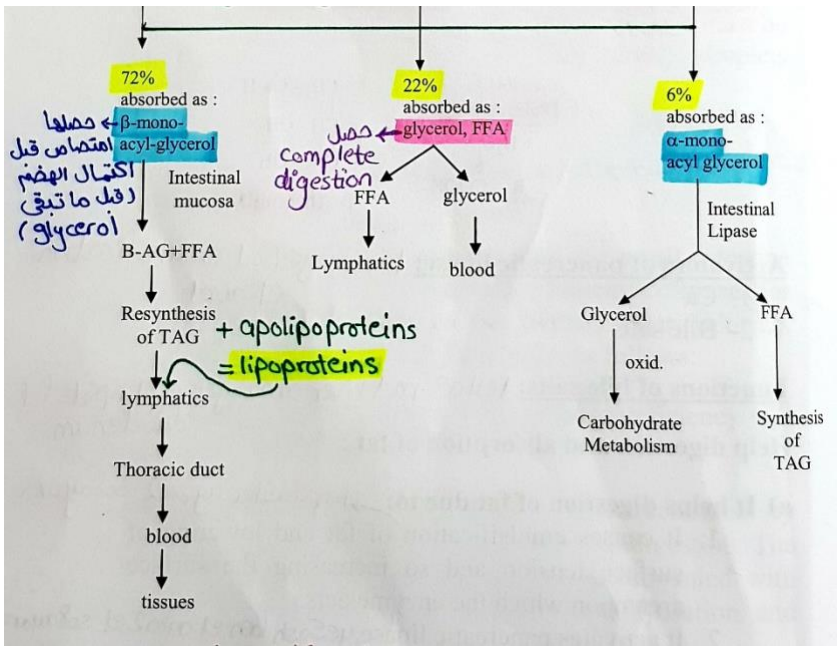
a) Apo-C-1 is present in VLDL and HDL and it activates LCAT enzyme
b) Apo-C-2 and Apo-C-3 are present in VLDL, HDL and chylomicrons
c) Apo-C-2 is an activator of lipoprotein lipase, which convert chylomicrons into remnants, and converts VLDL to LDL (both actions in EHT)

4-Apoprotein E and D:

E is used in the mobilisation of cellular cholesterol and stimulation of lipoprotein lipase enzyme (found in EHT)

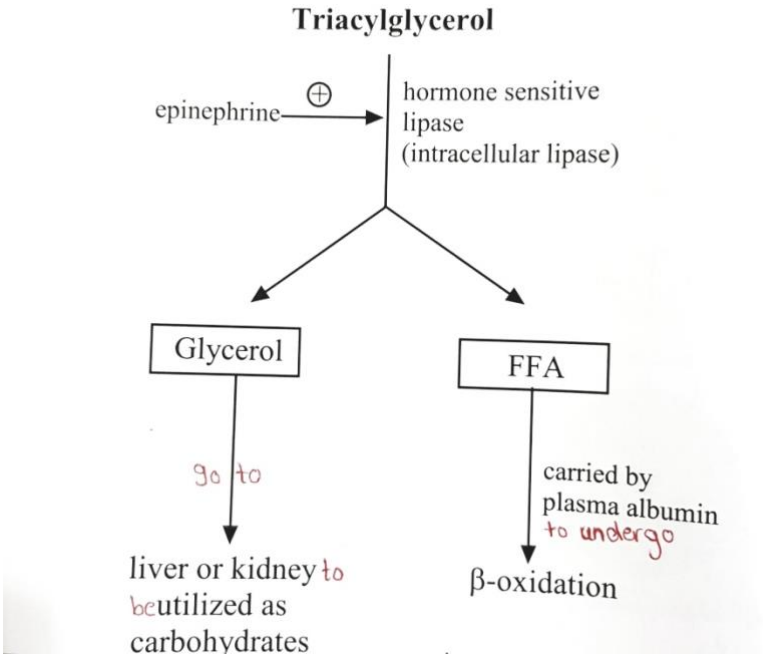
اهم ٤ نزكز بزيادة اوي عليهم هم Apo-b-48,Apo-b-100,Apo-C-2 and Apo-E

Absorption of Triacylglycerols (3 typesof adsorption)



Lipolysis

Hydrolysis of triacylglycerol in adipose tissue is **due to the action of intracellular lipase** enzyme which is sensitive to hormones (as epinephrine) ,leading to **release of free fatty acids (FFA) and glycerol (mobilization from adipose tissue)**



B-Oxidation of fatty acids
“saturated fatty acids"
“knoop's theory"

●It takes place by breaking the double bond at Beta carbon (more common in our body than alpha-oxidation)

●First, **triacylglycerol is metabolised into glycerol + fatty acids**, then fatty acids are **oxidized to acetyl-CoA** in The mitochondrial Matrix ****not in cytosol**

●It is an aerobic process only which requires the presence of oxygen

●It's the main source of energy during **fasting** and **starvation**

●Its pathway:-

●Fatty acids **must be activated** before entering mitochondria and before they can be catabolized, **this is the only step which needs ATP**

1-The Enzyme **thiokinase** activates the fatty acid by adding CoA enzyme to it, **to form active fatty acid which is then called “acyl-CoA"** , so it requires the presence of CoASH and ATP

الطبيعي ان احنا لما بنستهلك ATP بيتحول لADP يعني كسرنا High energy bond واحده
واخذنا phosphate واحده لكن المرادي الانزيم ده بيستهلك واحده بس لكن بيكسر ربطتين و بيطلع منها اتنين phosphate و تتحول ل AMP فا كأننا استهلكنا اتنين ATP

طب دلوقتي بعد ما عملناله activation, ايه اللي ها يمنعه من انه يخش الميتوكوندريا ؟ للاسف الجدار الداخلي للميتوكوندريا مش بيدخل الlong chain acyl-CoA فلازم يجي ٣ انزيمات تساعدوانه يدخل، و الmechanism بتاعهم اسمه Carnitine Transporter

2-Carnitine Transporter:

a)Carnitine-acyl-transferase-1

Acyl يعني fatty acid فلو هنتكلم مثلا عنpalmitic acid يبقى الانزيم ده هيبقى اسمه:

Carnitinepalmitoyl-transferase-1و هنكمل باقي الشرح عال palmitic acid دا

●This enzyme is present in the **outer membrane** of the mitochondria

● Palmitoyl CoA (acyl CoA) binds with this enzyme to be **converted to palmitoyl carnitine, and CoA is released**

كده احنا عدينا من الجدار الخارجي

2)Carnitine palmitoyl-carnitine translocase

الانزيم ده ليه ايدين، ايد تمسك في الcarnitine اللي عند الجدار الداخلي وايد تمسك في الpalmitoyl carnitine اللي اتعمل في اول خطوة عند الجدار الخارجي ويقوم يلف لفة فا يخرج اللي جوه لبره ويدخل اللي بره جوه (عند ال جدار الداخلي)

3) carnitine palmitoyltransferase II

●It's found in the **inner membrane of mitochondria**

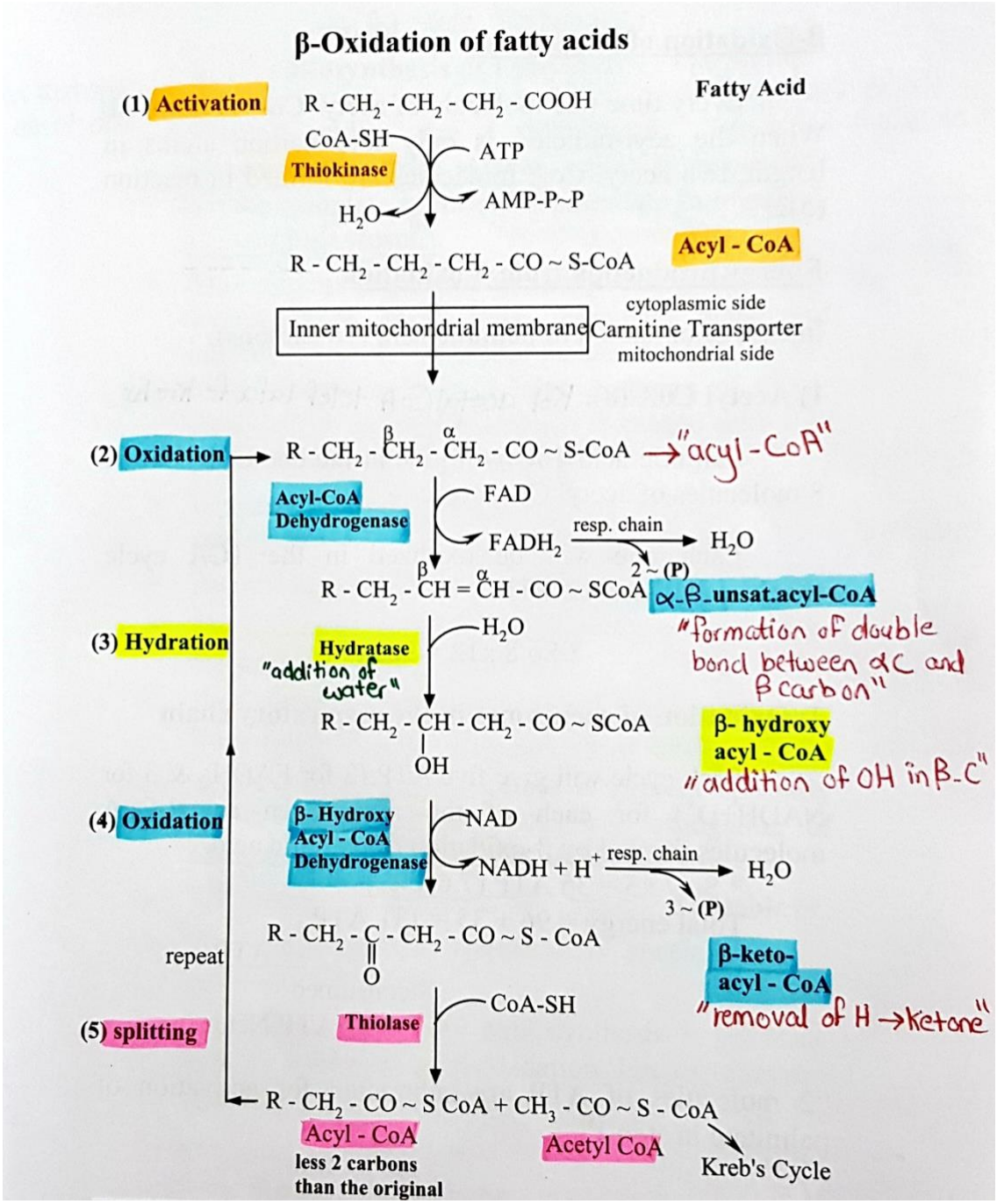
●It **removes carnitine from palmitoyl-carnitine**, and then re-binds CoA to the palmitoyl again **to give palmitoyl CoA (and carnitine is released)**

يبقى احنا كده قدرنا ندخل الpalmitoyl CoA جوه الميتوكندريا

The summary of carnitine transport:

1) Carnitine and a specific enzyme “transferase 1” help the transport of long-chain fatty acids through the inner mitochondrial membrane to reach the mitochondrial Matrix in the form of acyl carnitine
2) Diffusion of acyl carnitine through the inner mitochondrial membrane to the matrix is helped by the enzyme translocase
3) Removal of carnitine and addition of CoA to the acyl molecule is done by transferase 2

N.B: Carnitine is (B-hydroxy-gamma-trimethyl ammonium butyrate), it's widely distributed, but more excess in muscles



1)في اول خطوه قلنا اننا بنستهلك واحدة ATP بس كأنها اتنين يعني خسرنا اتنين ATP

٢)في تاني خطوة طلع FADH2اللي هايطلع 2 ATP

٣)في رابع خطوة طلع NADPH+H اللي هيطلع 3 ATP

يبقي كدة في ال cycleدي طلع اجمالي 5 ATP، و في الاول خسرنا و استهلكنا اتنين يبقي في اللفة الواحدة من الخمس خطوات دول هايطلع 3ATP بس

٤)في الخطوة الاخيرة كل مرة يحصل فيها splitting بيطلع واحدة بس acetyl CoA اللي بتتكون من carbons only 2 ، و كل acetyl CoA هاتروح للKrebs cycle زي ماخدنا في الجلوكوز، فا دلوقتي لو قولنا مثلا ان palmitic acid فيه ١٦ كربونة، و في كل لفة من ال ٥ خطوات اللي فوق دول هايطلع من البالميتيك Acetyl coAواحدة اللي فيها ٢ كاربون، يبقي هايطلع كام acetyl CoA؟ نقسم ١٦ علي اتنين يبقي هايطلع ٨، يبقي كده هنحتاج نعيد الخمس خطوات اللي فوق دول كم مره عشان نخلص ال 16 كربونة بتوع البالميتيك ؟

٨؟ غلط. ليه بقا؟ لان اول ست لفات كل مره هيطلع 2 فكده هيبقى 12 كربونة، طب والسبعه بقى؟ هايتبقالي اربعه من ال 16، فا دول ب split واحده هتقسملي الاربع كاربونات كل اتنين مع بعض، يعني بخطوه واحده طلعنا 2 acetyl CoA في نفس الوقت، يبقى كده عشان اخلص ال 16 كربونة بتوع الpalmiticهنعمل الخمس خطوات دول 7 مرات بس مش8 ،يعني بنشوف عدد الكربونات اللي في ال fatty acidاللي قدامنا ايا كان هو ايه ونقسمه على اتنين ونشيل واحده.

The summary:

1) Everytime (every cycle), **one molecule of acetyl CoA is released**
2) When the acyl radical **becomes only 4 carbon atoms in length** (the last 4 carbons), 2 acetyl-CoA molecules are formed in the same reaction **with one split**

Energy production from beta oxidation:

In case of palmitic acid:

1) **Acetyl CoA (8)**
   Palmitic acid will give at the end of oxidation 8 molecules of acetyl CoA
   Each one will be oxidised in the krebs cycle and give 12 ATP
   كل واحده هتخش ال krebs cycleو تلف لفه واحدة بس تطلع فيها 12 ATP
   So, 8×12= 96 ATP
2) **Oxidation of coenzymes in the respiratory chain**
   Each cycle will give 5 ATP, 2 from FADH2 and 3 from NADH+H (in case of palmitic the cycle will be repeated 7 times)
   So,5×7=35 (then we will remove the 2 ATP consumed at the first step)
   So, the net gain is 33+96=129

Q)T or F:

In the step of activation,one molecule of ATP is consumed (F)

هاتبقي ٢ لأننا كسرنا اتنين phosphate ،و اكبر دليل اننا في الnet result عملنا 2- ATP

Biosynthesis of Fatty acids
"lipgenesis"

● it occurs in the **fed state** (بعد الاكل علطول)
1)to be stored in the body
2)and lipids could be utilised when energy is needed (when there is no glucose)

● fatty acids are synthesized by an **extramitochondrial system** (cytosolic system), which is responsible for the complete synthesis of palmitic acid from acetyl CoA

Extramitochondrial system:
● this system is **the most important system**, and is present in many tissues including liver, kidney, brain, lung, mammary gland (in lactic acid) and adipose tissue

● when this system **abnormally increases**, it causes obesity; due to excess formation of fats

● it's cofactors include **NADPH, ATP, Mn^{+2} , biotin and HCO3** (source of CO2)
***Cofactors=** العوامل المساعدة

● Acetyl CoA is the immediate and main substrate for the reactions, and free palmitic acid Is the end product
***subsrate=**المركب اللي بيبدأ التفاعل

● **it is stimulated by insulin**, and therefore it is **inhibited in diabetes mellitus type 1** (when there is insulin deficiency)
● It needs a specific **multienzyme complex** called **fatty acid synthase complex** and also needs an acyl carrier protein **"ACP"** (protein that carries fatty acids)

● the **first reaction in this system is carboxylation** (adding COOH) for acetyl CoA (which is arised from pyruvate of glucose) **to malonyl CoA**, and this step needs ATP
● and later, **two carbons will be added** from each Malonyl CoA **to the acetyl CoA** (will be explained later)

احنا جسمنا ما يقدرش يصنع اكثر من 16 كربونه في الfatty acid وما يقدرش يصنع fatty acid عنده اكثر من واحده double bond، يعني يقدر بس علي mono unsaturated fatty acid، يعني اي حاجة غير كدة هاتبقي essential زي ال PUFAمثلا.
طب لو انا محتاجه في جسميfatty acid يكون عنده اكثر من 16 ويكون عنده اكثر من واحدة double bondنعمل ايه؟ في systems 2 تانيين بيعملوا elongation لل ١٦ تبقي ١٨ مثلا بأنه يزود كربونتين كمان بس، و كمان يقدروا يزودوا عدد الdouble bonds و اسمهم
mitochondrial and microsomal systems

●The microsomal system is present especially for elongation of fatty acids ex: **elongation of palmitic acid to stearic acid (18 C)**

● mitochondrial system is also present and it acts especially under **anaerobic conditions**

● the mechanism and reactions of fatty acid synthesis is somehow **reversing of the Beta oxidation** but the enzymes and coenzymes are different

Study this table well:

Table (3) : Synthesis of fatty acids

site	1- Mitochondrial	2- extramitochondrial (cytosol)	3- Microsomal
The formed fatty acid	• Eleongation of long chain F.A. • Palmitic 16C • Stearic 18C	Synthesis of palmitic acid	Elongation for pre-existing F.A molecule (10-16C)
the substrate	Adding 2C each time from acetyl CoA	Needs acetyl CoA (primer) & malonyl CoA	2C added from malonyl-CoA
mechanism	Reversal of β-oxidation	Every time 2C added (from malonyl CoA)	Steps as any synthetic pathway → adding 2C → F.A + 2C more
Source of energy	NADPH needed for "reduction of α-β-unsaturated acyl CoA step" & reductase	NADPH is needed from : • Malic enzyme • HMP pathway	NADPH needed for reductive steps
conditions	Only under anerobic conditions	• Enzyme system : "F.A synthase" • Acyl carrier protein • Multienzyme complex	Inhibited by Fasting

• mitochondrial and microsomal can be alternatives for synthesis of another fatty acids other than palmitic acid by elongation and desaturation of palmitic acid.
• HMP pathway equals pentose phosphate pathway

The fatty acid synthase complex is a polypeptide containing seven enzyme activities:

●the synthase system is a multi-enzyme polypeptide complex that contains ACP (acyl carrier protein), which takes over the role of CoA

ACP دا حاجه شبه الCoA وبتاخد دورها

●It is a dimer that consists of **two identical monomers attached to each other head to tail**, and each monomer **contains 7 enzymes on one polypeptide chain**

● it contains the vitamin pantothenic acid in the form of 4-phosphopantethiene, And this enzyme is important in fatty acid synthesis **because it produces the ACP**

●The use of one multienzyme functional unit has the advantages of achieving the effect of compartmentalization (division) of the process, and synthesis of all enzymes in the complex is coordinated since it is encoded by the same gene

يعني كل واحد فيه multienzyme system يخليه يقدر يشتغل لوحده لو حصل تقسيم لل 2 monomers، و تصنيع كل الانزيمات متناسق و مع بعضه لأن نفس الgene بيصنعم

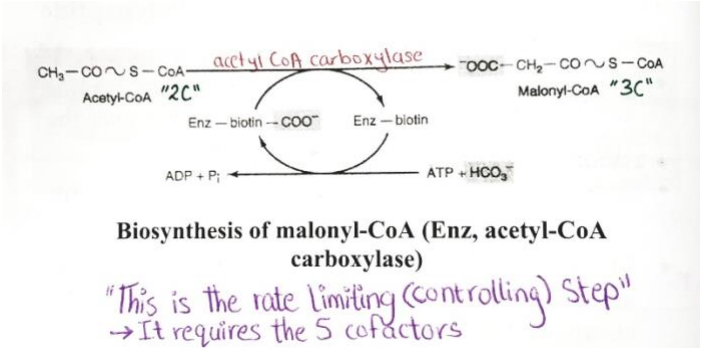
● palmitic acid is formed at the end of the pathway

● in Palmitic acid, the first formed 2 carbons (no. 15 and 16) are added **by a primer acetyl CoA**, and then the addition of subsequent 2 carbon units are added **by malonyl Co-A** (will be explained in further details now)

The pathway:

For example synthesis of palmitic acid:

1- Carboxylation of acetyl CoA (2 C) takes place to form malonyl CoA (3 C) (This is the most important and the main step)



Biosynthesis of malonyl-CoA (Enz, acetyl-CoA carboxylase)

"This is the rate limiting (controlling) step"
→ It requires the 5 cofactors

2- A priming molecule of acetyl CoA combines with a **cysteine-SH group in one of the two monomers,** and this is catalyzed by acetyl transacylase

3- Malonyl CoA combines **with the adjacent-SH** on the 4-phosphopantethiene of ACP of the other monomer, and this is catalysed by malonyl transacylase; **to form acetyl (acyl) malonyl enzyme**

يعني acetyl CoA تمسك في SH group في monomer من الاتنين و الmalonyl تمسك في ال SH في الmonomer التاني و بعدين كدا هايتكون انزيم اسمه acetyl malonyl enzyme دا هايمسك في ال acetyl CoA والmalonyl CoA و يربطهم ببعض فا بكدة يبقي عندي ٥ كربونات

4- An enzyme called 3-keto acyl synthase releases CO2 from the 5 carbons leaving 4 carbons only **(3-keto acyl group)** (it removes the carbon of CO2 from malonyl not acetyl CoA) , this 3-keto acyl group will be reduced then dehydrated then reduced again to form saturated acyl S enzyme

يبقى احنا كده اهو حطينا اول اربع كربونات من ال 16، و رقم 16 و 15 من ال acetyl CoA

5-Step 4 will be repeated by continuous addition of malonyl CoA and removal of CO2 from it, **so each time and each molecule of malonyl CoA adds 2 carbons**

يعني احنا في اول لفه حطينا اربعه من ال 16 يبقى اتبقى 12، وفي كل لفه بقينا نزود 2 بس يبقى كده اتبقي 6 لفات، يبقي كده الاجمالي سبع لفات زيها زي ال B-oxidation بس الفرق ان هنا اول خطوه حطينا 4 وهناك كانت اخر خطوه هي اللي اتبقى فيها الاربعه

Metabolism of Ketone bodies

Ketone bodies are organic acids formed mainly in the liver in very small concentrations, and may be formed in other tissues

Types of ketone bodies:

1- Aceto-acetic acid
2- Acetone
3- B-hydroxybutyric acid

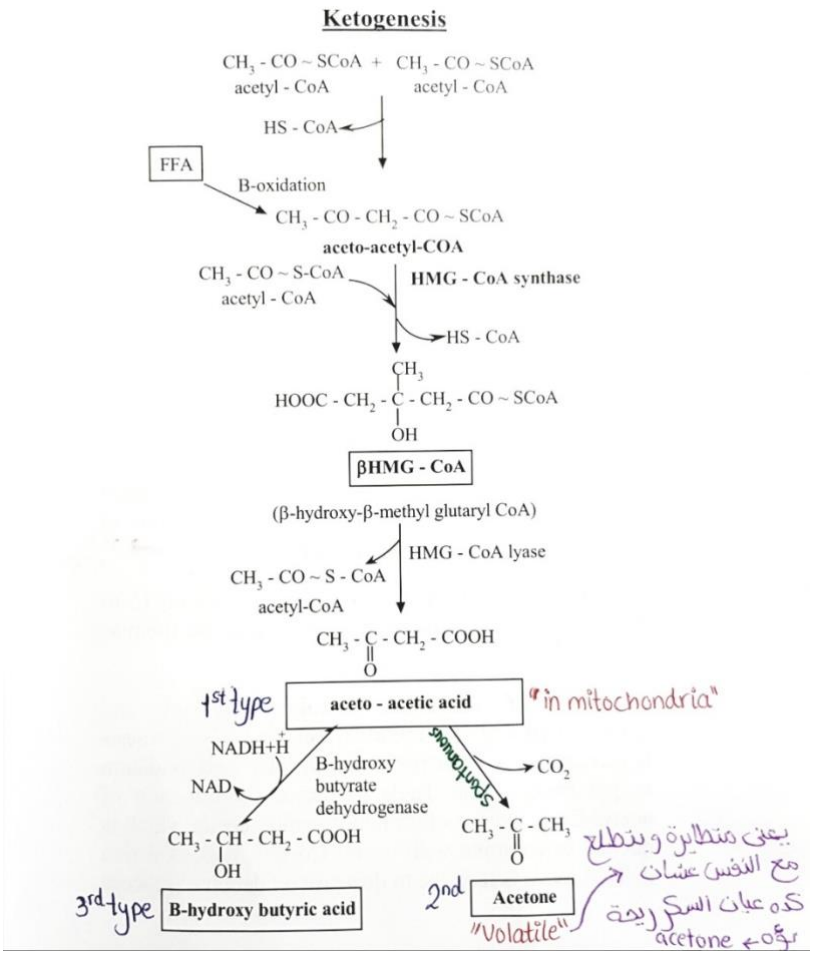
Normal level in blood is 1.5-2 mg% (if increased, acidosis occurs)

Ketogenisis:

لما ييجي جسمنا بيبدا يكسر في الدهون ويطلع 129ATP بتكون كميه كبيره قوي واحنا مش محتاجين كل ده فحبة من ال acetyl CoAيتحولوا لketone bodies و لو احتاجنا طاقة تاني ساعتها نكسر الketone bodies

- synthesis of ketone bodies occur in the liver and all tissues (but more in liver)
- **it's main substrate is acetyl CoA** (This acetyl coA comes from **oxidation of fatty acids** or **ketogenic amino acids** but not from glycolysis)
- 3- hydroxy-3-methylglutaryl-CoA (HMG-CoA) is an intermediate in the pathway of ketogenesis
- enzymes responsible for ketogenesis are associated mainly with the mitochondria

Pathway:



- two molecules of acetyl-CoA (that are formed in oxidation of fatty acids) condense together to form acetoacetyl-CoA **(by a reversal of thiolase action)**

بدل ما يحصلهم splitting هايتجمعوا مع بعض (بعكس ال thiolase اللي كان بيكسر في ال-B oxidation)

● the acetoacetyl CoA is the starting material for ketogenesis, and it can directly arise from the last four carbons of a fatty acid during beta oxidation

يعني ممكن يجمع اثنين acetyl CoA مع بعض او ياخذ اخر اربعه اللي كانوا مع بعض فال-B oxidation مره واحده قبل ما يشتغل عليهم ال thiolase

● condensation of acetoacetyl-CoA with another molecule of acetyl-CoA takes place by 3-hydroxy-3-methylglutaryl-CoA **synthase** enzyme; **to form HMG-CoA**

●3-hydroxy-3-methylglutaryl-CoA **lyase** then causes acetyl-CoA to split off from HMG-CoA, **leaving free acetoacetate** (the 1st type of ketone bodies)

●both enzymes must be present in **mitochondria** for ketogenesis to take place, **this occurs only in liver**

في ال ketogenesisالخطوات كلها بتحصل في ال liverواال EHT لحد قبل تصنيع ال HMG-CoA علطول ، يعني لحد قبل الانزيمين دول، ال EHT بيوصل لحد الخطوتين دول و يبعت اللي عملوا لل liver يكمل هو الketogenesis، طب ليه مش ال liverالوحده اللي يعمل الخطوات دي من اولها لاخرها طالما كدة؟ لان الخلايا بتصنع cholesterol بنفس الطريقة وساعتها بتصنع ال HMG-CoA كمان لكن بعد ال HMG-CoA بتكمل خطوات تانية غير ال acetoacetate fromation ،يعني كل الخطوات لحد بعد تصنيع ال HMG-CoAبتحصل في كله بس لو cholesterol هايبي اللي بعد ال HMG-CoA في الEHT بس، و لو ketogenesis، ال HMG-CoA مش هايتكون غير في ال liver

So, ketogenesis is done and completed only by liver

●the carbon atoms that are split off in the acetyl-CoA molecule are derived from the original acetoacetyl-CoA molecule

يعني احنا دلوقتي على ال acetoacetyl-CoA حطينا acetyl CoA و رجعنا تاني شلناه ، طب ايه الفايدة بقي؟

احنا لما حطيناهم على بعض بقى عباره عن حاجه واحده ما اقدرش اميز حاجه عن الثانيه، لما جينا نفرقهم ثاني الانزيم اللي اشتغل عليهم عايز يطلع acetyl-CoA و خلاص مش مهم عنده يكون الكربونات منها من انهي مركب فيهم عشان بقو بنسباله حاجة واحدة، بس بنسباله الكربونات اللي هايعمل بيها acetyl-CoA عشان يبقي removed كان اسهله ياخدها من ال acetoacetyl، فا بكدة شلنا الCoA دي منه فا اتحول لacetoacetic acid

●Then the acetoacetate will produce the other 2 types of ketone bodies in mitochondria as shown in the figure above

●B-hydroxy butyrate is the most predominant ketone body present in blood and in urine in ketosis

Regulation of ketogenesis:

1- **By controlling of free fatty acid mobilization from adipose tissue** (when glucose and insulin increase, ketogenesis decreases)
N.B:insulin stimulates lipogenesis and inhibits lipolysis
2- **By the activity of carnitine transferase in liver**, which determines the amount of free fatty acid passing to the matrix of the mitochondria from cytosol that will be oxidized (when the amount increases ketogenesis increases)
3- **Distribution of acetyl-CoA between the pathway of ketogenesis and the citric acid cycle** (when energy needs increase, acetyl CoA will pass more to the krebs cycle to produce energy and so, ketogenesis decreases)

Ketone bodies serve as a fuel for EHT:

While and active enzymatic mechanism (HMG) produces acetoacetate from acetoacetyl-CoA in the liver, acetoacetate once formed, cannot be reactivated directly **(except in the cytosol),** where it is used in a much **less active pathway as a precursor in cholesterol synthesis (small number)**, but majority produce energy, and this accounts for the net production of ketone bodies by the liver

Ketosis:

●increased fatty acid occurs in cases of **starvation** and **diabetes mellitus,** leading to ketone body production by the liver “ketosis"

●KB in ketosis abnormally appear in urine causing “ketonuria"

●ketone bodies are acidic, so in diabetes mellitus when they are produced in large amounts over long periods , **they cause ketoacidosis** (ketosis+acidosis)

●keto-acidosis is fatal due to depression of respiration and inhibition of brain centers leading to coma and maybe death

●**when people fast for 5-6 days,** brain tissues benefit from oxidation of ketone bodies, and use them as main fuel and source of energy (because **ketone**

bodies can cross the blood-brain barrier to supply it with energy. (Unlike fatty acids which cant))

●**in cases of starvation, insulin deficiency and uncontrolled diabetes mellitus, KB synthesis is increased** due to increased rate of fatty acid oxidation to get energy, this leads to increase production of acetyl CoA, on the other hand, oxalo-acetate which is needed to combine with acetyl CoA to start oxidation in TCA cycle (krebs cycle) is less; **due to decreased oxidation of glucose** (either due to insulin deficiency or glucose deficiency), so acetyl-CoA is deviated to ketogenesis

احنا كنا خدنا قبل كده ان في حاجة اسمها oxalo-acetate بتطلع من الجلوكوز و بتمسك في ال acetyl-CoA عشان يدخلkrebs cycle، طب دلوقتي في الحالات دي يعتبر مفيش جلوكوز اصلا فا مفيش oxalo-acetate فا الacetyl CoA هاتروح معظمها تصنع KB بدل ما تدخل krebsعشان تطلع طاقة

Summary for Causes of ketosis:

1- Uncontrolled diabetes mellitus
2- Low carbohydrate diet: leads to decreased production of pyruvate and oxalo-acetate so, Acetyl CoA arising from B-oxidation of fatty acids will condense to form KB
3- Starvation
4- Increased intake of fat in diet, which leads to increased production of acetyl CoA from increased oxidation of fatty acids
5- Factors leading to loss of glucose in urine, such as: renal glucosuria and phlorhizin poisoning
6- It may occur in pregnancy, specially when they are twins, and more common in animals as sheep