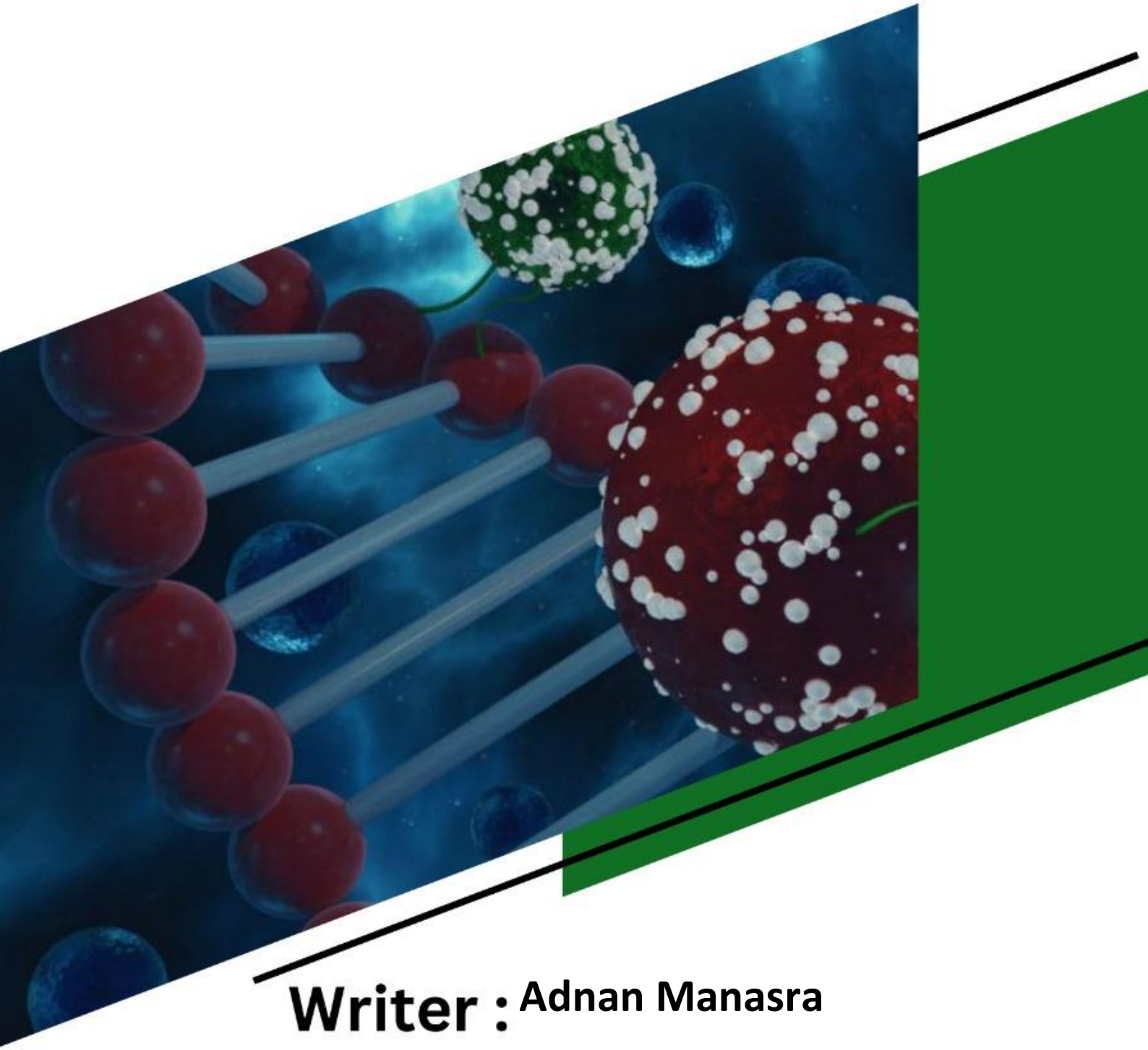
Doctor 021

METABOLISM

Sheet no. 22



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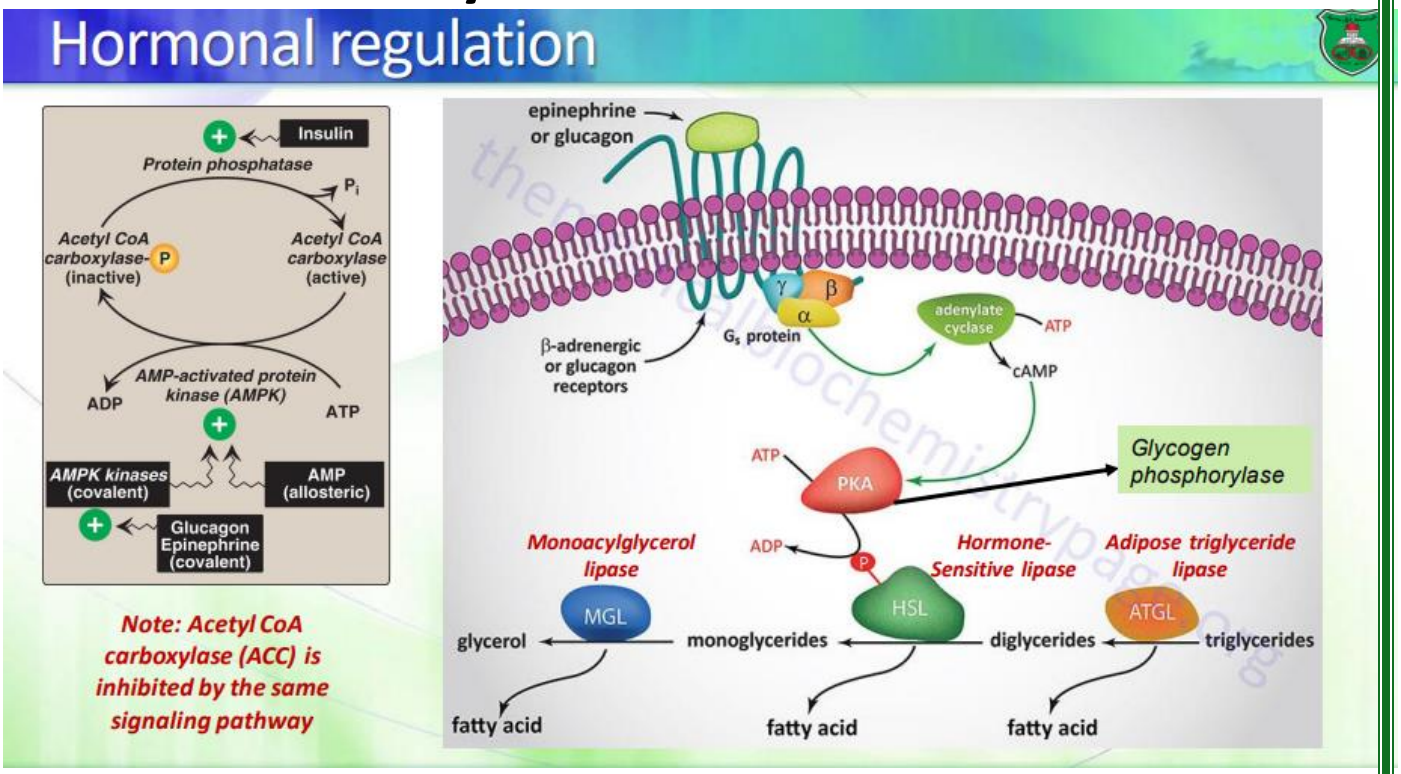
**** I know it is a very long sheet , but when you study it you will find that it is an easy concept , but it needs to be clarified perfectly . wishing you all the best dears.**

Degradation of fatty acids

After we learnt how the body synthesize fatty acids , in this lecture we are going to talk about how fatty acids are broken down to produce energy .

as an introduction to our concept ,lipids are rich in energy and it is the best energy storage molecules (long term storage molecules), and the most common type of lipids is TAG (triacylglycerol) either we take it from food or synthesized and stored by our body.
As we know , TAG are composed of glycerol and 3 fatty acids , so we need to break down this TAG to have free fatty acids and then break down these fatty acids to produce energy, so how this process occurs ?

- Release of fatty acids from TAG



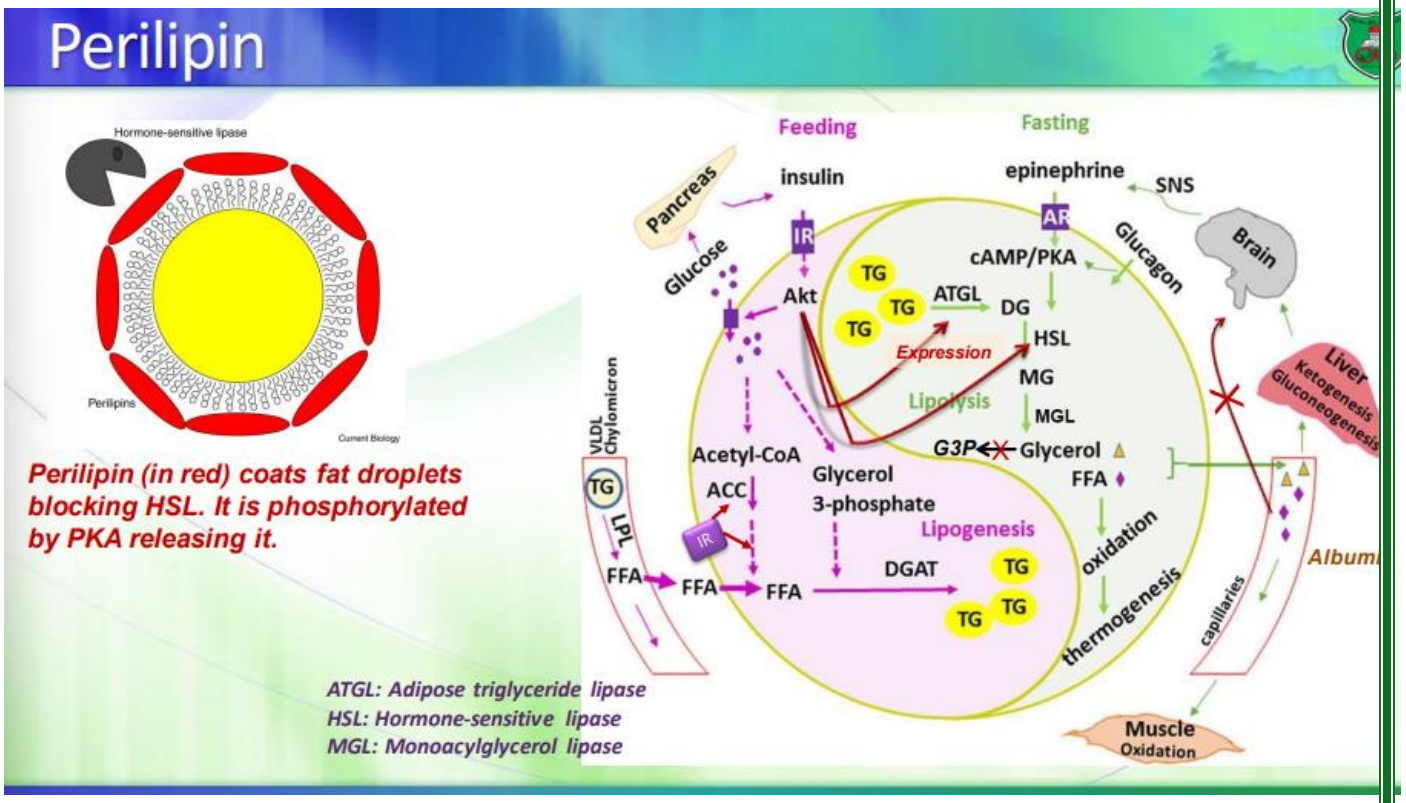
as you can see in the figure above , this is the mechanism of releasing fatty acids from TAG , how it starts ?

The body sends signals to the liver and adipocytes that it (the body) needs fatty acids which are on TAG in the adipocytes , so the glucagon hormone (or the epinephrine in the muscles) binds to its receptor and activate it > the receptor activates G protein > activating adenylate cyclase > increasing cyclic AMP in adipocytes > cAMP makes an activation to the enzymes which are responsible of releasing fatty acids from the TAG , especially the HSL (hormone sensitive lipase) .

Then the mechanism happens as follow :
triglycerides become diglycerides by an enzyme called ATGL (adipose triglyceride lipase) and releasing 1 fatty acid > diglycerides become monoglycerides by an enzyme called HSL and releasing 1 fatty acid > monoglycerides become glycerol by an enzyme called MGL (monoacylglycerol lipase) and releasing the last fatty acid .

* HSL is under regulation of protein kinase A (PKA) which is activated by cAMP and its level increases when there is epinephrine or glucagon .

* PKA makes phosphorylation to HSL and ACC (the enzyme which is responsible of synthesize of fatty acids) so it activates the HSL and inhibit the ACC at the same time (it is illogical to make synthesizing and degradation for the same molecule at the same time) .

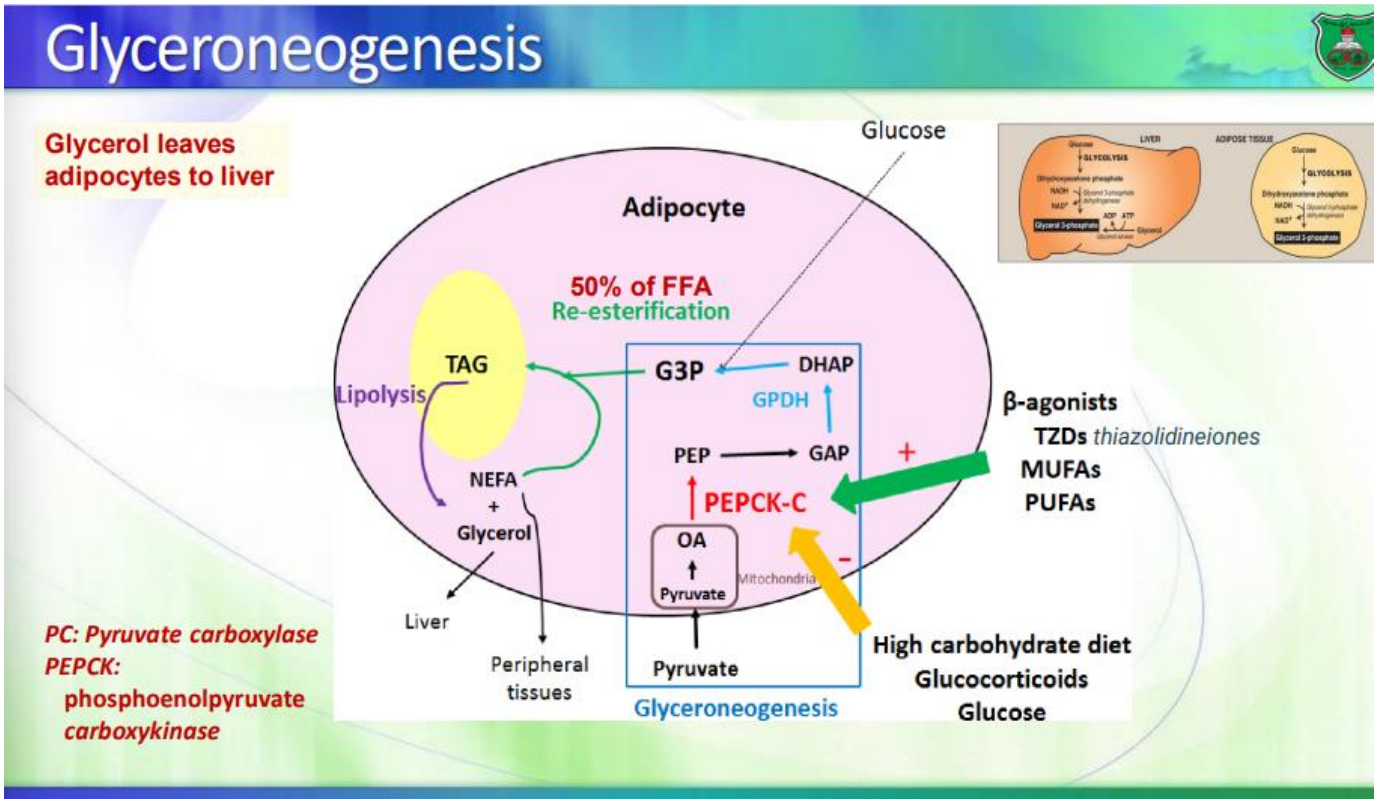


in case of fasting , glucagon and epinephrine work to produce energy by activating HSL …

in case of feeding , insulin binds to its receptor and inhibits synthesis of ATGL and inhibits the activity of HSL by activation of phosphatase , which release the phosphate groups , also insulin activate the entry of fatty acids to cells to make TAG .
*** So insulin inhibits the lipases (not activate it) via the phosphatase .

look at the figure above , Perilipin (in red) , it is a structure that coats fat droplets in adipocytes , which blocks the activity of HSL , so it is phosphorylated by PKA to release it .

NOW , we have 3 free fatty acids which will bind to albumin and go to peripheral tissues and the glycerol will go with blood to the liver.



Recent studies proved that we have synthesis of glycerol in adipocytes by a process called Glyceroneogenesis .
when we release fatty acids from TAG , the glycerol goes to the liver and the fatty acids go with albumin , but , up to 50% of fatty acids will have re-esterification (resynthesizing TAG by binding fatty acids with glycerol by ester bonds) , but the question here is why to do this process ?
the body regulates the amount of free fatty acids in the blood , so without this process the amount of free fatty acids in the blood will be high and this is not good for the body (it is a protective mechanism by the adipocytes) .
But as we mentioned before , the glycerol left to the liver , so how we can make re-esterification (TAG synthesis) , and we have starvation so we don't have glucose to make glycerol ? what is the solution ?
The solution is (Glyceroneogenesis) : formation of glycerol from pyruvate in adipocytes .
cells take lactate and amino acids from Krebs cycle and convert them into pyruvate > pyruvate is converted to OA (oxaloacetate) > OA is converted to phosphoenolpyruvate PEP > PEP is converted to

glyceraldehyde 3 phosphate > glyceraldehyde 3 phosphate is converted into dihydroxy acetone phosphate > dihydroxy acetone phosphate is converted into Glycerol 3 phosphate which is used as a back bone for fatty acids , (gluconeogenesis) .
simply the cells take the glycerol from the " gluconeogenesis " pathway , and this what we call Glycroneogenesis .

* The enzyme phosphoenolpyruvate carboxykinase PEPCK-C is responsible of converting OA into PEP , and it is regulated by :

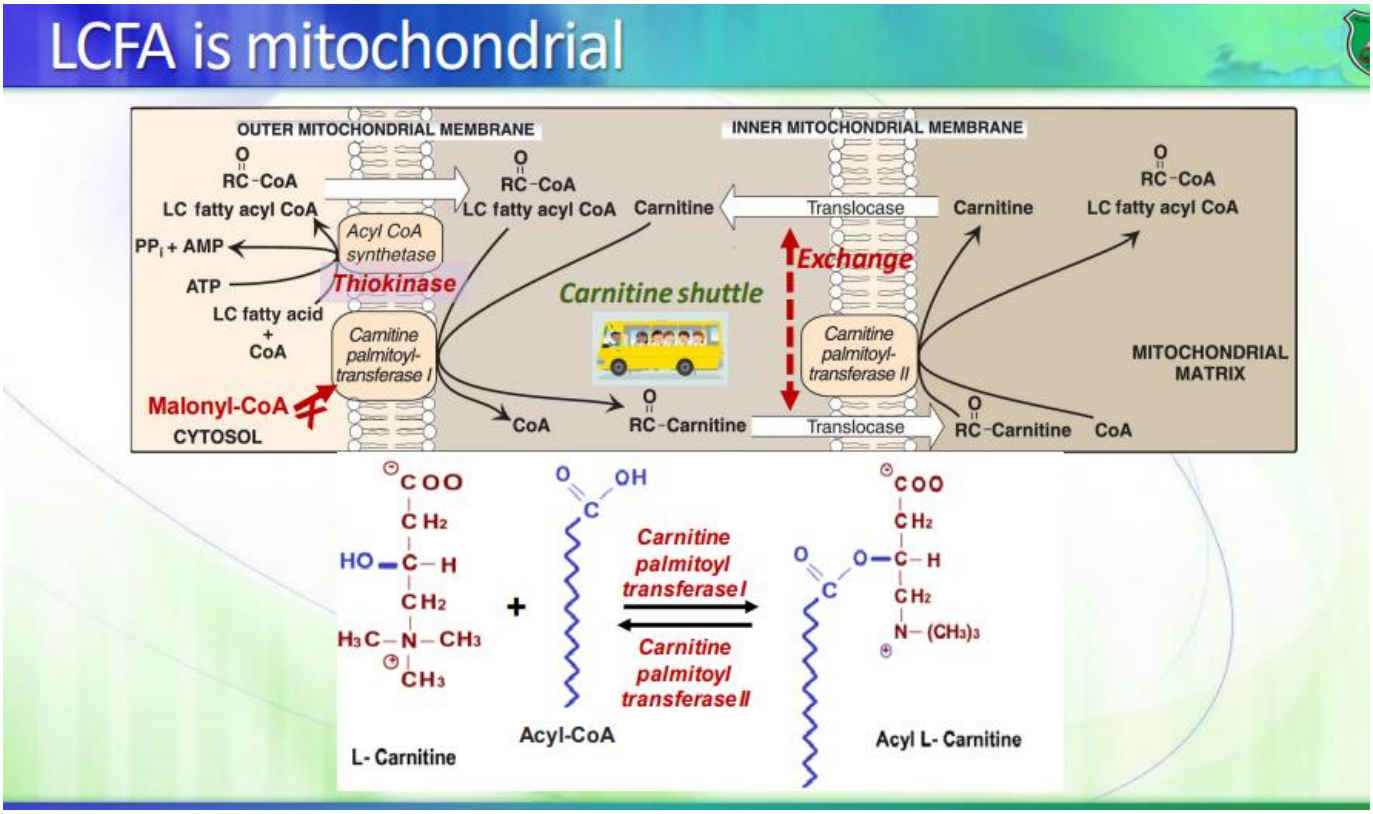
1. Activated by monounsaturated and polyunsaturated fatty acids .
2. It gets inhibited by high carbohydrate diet or glucose .

Fatty acids oxidation … Beta oxidation

Means breaking down of fatty acids

Previously, we talked about degradation of TAG which is the process for cleavage and separation of fatty acids from glycerol in a TAG molecule... Now we get these fatty acids and we want to break them down
The idea here is when you have beta oxidation, you have the release of 2 carbons in a form of Acetyl CoA and this takes place in the mitochondria (mitochondrial matrix), fatty acid synthesis takes place in the cytosol (there is a separation of these two opposite pathways) .

So we have the production of Acetyl CoA from the breaking down of fatty acids, and this Acetyl CoA goes to the Kreb's cycle (you know the pathway) .



Let`s talk in details about beta oxidation :

Now , we reach a stage that we have free fatty acids (palmitic acid) in the cytosol , so we need to transport them to the mitochondria (to the matrix of mitochondria) in which the beta oxidation (B-oxidation) takes place .

Firstly , we need to activate the fatty acids which means we need to make the fatty acids high energy bond molecules , by binding it to CoA so it becomes fatty acyl – CoA , through an enzyme called CoA synthetase (or thiokinase) which is located on the outer membrane of the mitochondria , and this molecule (fatty acyl – CoA) enters to the intermembranous space .
This process needs energy and we take this energy from hydrolyzing ATP to AMP and you will have the release of pyrophosphate .
* Note : by converting ATP to AMP , it is like hydrolyzing 2 ATP molecules .

But as we know , the inner membrane has a high impermeability , so we can not proceed to the matrix .
because of that , the fatty acyl – CoA binds to carnitine (a structure you can imagine it as a car) by an enzyme located on the outer membrane called CPT 1 (carnitine palmitoyl transferase 1) , this enzyme cleave the CoA and replace it with carnitine , now the fatty acyl-carnitine enters to the matrix through translocase .
in the matrix , we will have exchange process , the carnitine is replaced with another CoA by an enzyme called CPT 2 (carnitine palmitoyl transferase 2)
and the resulting free carnitine will return to the intermembranous space but on one condition which is entry of another fatty acyl – carnitine and we call that carnitine shuttle system .

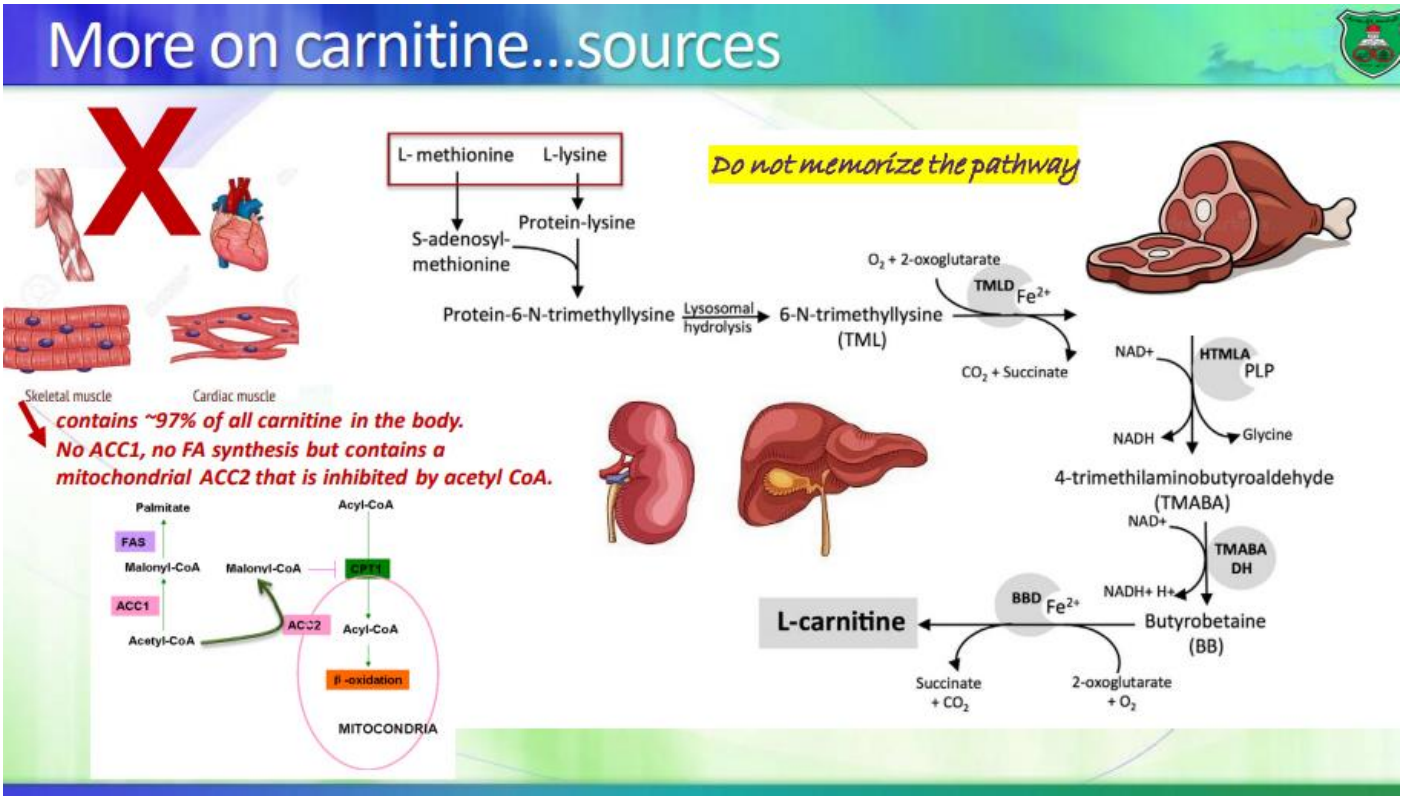
* Note : here we are talking about long chain fatty acids , small and medium chain fatty acids have easy entry to the matrix without these processes .
CPT 1 is inhibited by malonyl – CoA
The malonyl – CoA (which is an intermediate for the first reaction of fatty acid synthesis) is an inhibitor for the degradation of fatty acids , that makes a sense!!! Because you don't want to get fatty acids into mitochondria if you have enough malonyl CoA (the rate limiting step in fatty acid synthesis), it means there is enough energy in the cells and there is no need to break down more fatty acids
so it is illogical to make synthesis and degradation for the lipids at the same time .
In the muscles , although there is no synthesis of fatty acids , but there is synthesis of malonyl – CoA by an enzyme called (isoenzyme ACC 2 , different (in synthesis and …) than ACC 1 which is located in the liver and adipocytes) , to work as an inhibitor for the degradation by

inhibiting the CPT 1,2 so this will inhibits the entry of fatty acids to the matrix , and this happens when there is high source of energy .

So the whole function or purpose of carnitine is to transport the fatty acid across the inner membrane.

The transport of the fatty acyl carnitine into the mitochondrial matrix is done in exchange of a free carnitine (it is really an exchanger!)

It takes the fatty acid inside and instead of that you have a transport or exchange of carnitine out of the mitochondrial matrix, this is known as carnitine shuttle... It is like the bus .
before we proceed , let`s talk about carnitine :



- We have two sources for the carnitine :

1. Synthesis : the Methionine and the Lysine are the precursors of carnitine .

The synthesis of carnitine occurs in the liver and the kidney , and b – oxidation occurs mainly in the muscles because it is the most tissues need energy , so the carnitine leaves the liver and the kidney to the cardiac and skeletal muscles because these muscles don't synthesize carnitine .

2. Meat : 97% of carnitine is present in the cardiac and skeletal muscles , these muscles depend on the fatty acids as a source of energy .

- ***Carnitine deficiencies***

1. Primary carnitine deficiency

Defects in a membrane transporter: No uptake of carnitine by cardiac and skeletal muscles and the kidneys, causing carnitine to be excreted.

Treatment: carnitine supplementation.

2. Secondary carnitine deficiency

Taking valproic acid (antiseizure) → decreased renal reabsorption

Defective fatty acid oxidation → acyl-carnitines accumulate → urine

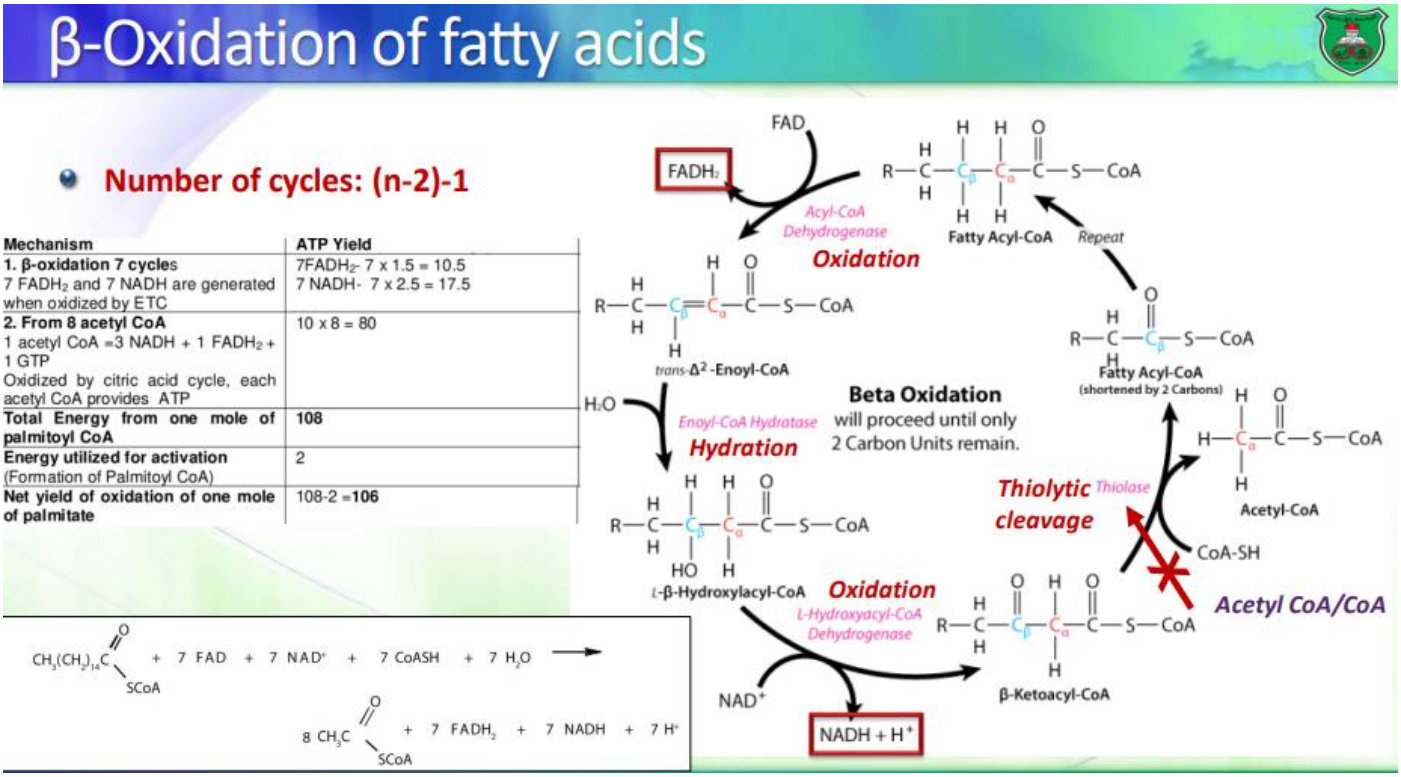
Liver diseases → decreased carnitine synthesis

CPT-I deficiency: affects the liver; no use of LCFA, no energy for glucose synthesis during fasting → severe hypoglycemia, coma, and death

CPT-II deficiency: affects the liver, cardiac muscle, and skeletal muscle
Treatment: avoidance of fasting and adopting a diet high in carbohydrates and low in fat but supplemented with medium-chain TAG.

* And in case of carnitine deficiencies , the largest dependent becomes on small and medium chain fatty acids (SCFAs , MCFAs) because their entry to the matrix does not depend on CPT 1,2 so SCFA and MCFA enter to the matrix easily and will be oxidized , unlike long chain fatty acids (LCFA) .

Now , we have reached the level that we have fatty acyl – CoA inside the mitochondria , and now we start what we really call beta oxidation :



* The fatty acid that we focus on is palmitate (16 carbon saturated fatty acid) .

The real beta oxidation reaction starts from the second step where we have fatty acyl CoA in the mitochondrial matrix.
The purpose of this process is to break the fatty acyl – CoA into acetyl – CoA molecules (2 carbons) , and this happens through a series of reactions .

The reactions in order are:

1. Oxidation reaction

2. Hydration reaction

3. Another oxidation reaction

4. Thiolytic cleavage

So these reactions really sort like a reverse of fatty acid synthesis (reduction / dehydration / reduction) .

* Please now in each step I am going to talk about , go back to the figure above and look at the chain in each reaction .

A. The first reaction is oxidation reaction by dehydrogenase, you have the production of FADH2 (the result is a compound with double bond)
look at the figure
so here we used electron carrier (FAD > $FADH_2$)

B. Hydration reaction (now you will get a compound with a hydroxy/ group that is attached to fatty acid)
look at the figure

C. Another oxidation reaction, you have the production of NADH. (Hydroxyl to keto group)
look at the figure
and here we used another electron carrier (NAD^+ > NADH)

D. Thiolytic cleavage (CoA attacks the fatty acid by using its terminal reactive group "Thio/ group SH-"
(Breaking the bond between alpha and beta carbons)
and it results in the releasing of Acetyl CoA (2carbons).
look at the figure

So you end up with a fatty acid that is shorter by 2 carbons (they are lost in a form of Acetyl CoA).

So the result of beta oxidation of palmitate is 14 carbon fatty acid and the process continues until we finish all the fatty acid and the acetyl CoA molecules go to Kribs cycle to produce energy

The electron carries (FADH2 / NADH) can be used in electron transport chain to produce energy.

* oxidoreductases and dehydrogenases need electron carriers (NAD^+, FAD)

Enzymes involved in this process (respectively) :

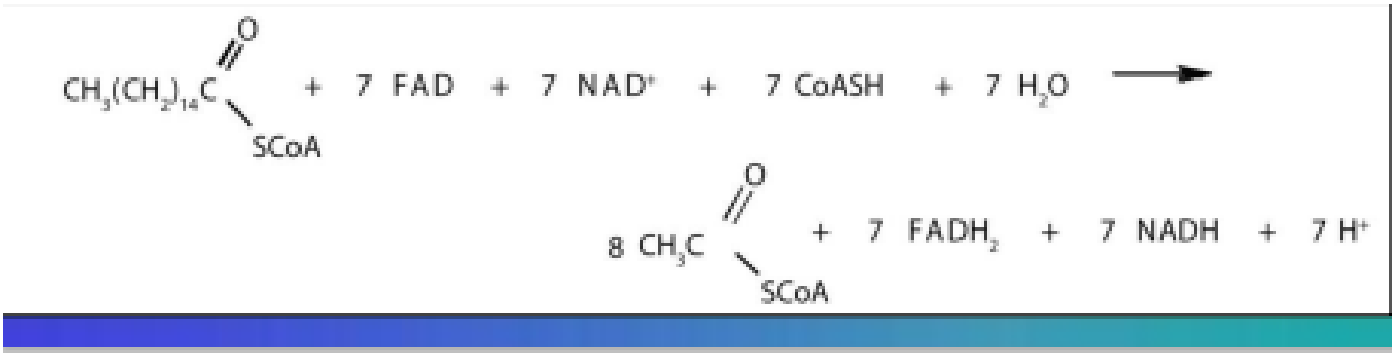
1. Acyl – CoA dehydrogenase
2. Enoyl – CoA hydratase
3. L-hydroxyacyl – CoA dehydrogenase
4. Thiolase

*** Why it is called beta oxidation? Because it involves beta carbon (the covalent bond between beta carbon and Alpha carbon is broken) , the beta carbon (which is in blue in the figure above , the third carbon) is oxidized (making double bond with oxygen) .

For a palmitate molecule (fatty acid) , how many cycles do we need? We need 7 cycles , why not 8 (it is 16 carbons) ?
Because at the end we have the production of butyrate (4carbons molecule), when it is cleaved you have the production of 2 Acetyl CoA molecules. Try to draw a chain with 16 carbons and cleave it several times in the way to get the whole 16 carbons are separated in segments each one contains 2 carbons and you will notice that we need to cut 7 times. So, you have the production of 8 Acetyl CoA molecules + 7 NADH + 7 FADH2

Number of cycles: (n-2)-1

Mechanism	ATP Yield
1. β-oxidation 7 cycles 7 $FADH_2$ and 7 NADH are generated when oxidized by ETC	$7FADH_2$- 7 x 1.5 = 10.5 7 NADH- 7 x 2.5 = 17.5
2. From 8 acetyl CoA 1 acetyl CoA =3 NADH + 1 $FADH_2$ + 1 GTP Oxidized by citric acid cycle, each acetyl CoA provides ATP	10 x 8 = 80
Total Energy from one mole of palmitoyl CoA	**108**
Energy utilized for activation (Formation of Palmitoyl CoA)	2
Net yield of oxidation of one mole of palmitate	108-2 =**106**



So how much energy can we produce?

Remember: we have 8 Acetyl CoA that will enter Kreb's cycle (every thing takes place in the mitochondrial matrix, so each Acetyl CoA produce 3NADH+ 1FADH2 + 1GTP that can be converted to ATP

You can multiply each NADH by 3 and each FADH2 by 2 however:

1 FADH2= 1.5 ATP

1 NADH = 2.5 ATP

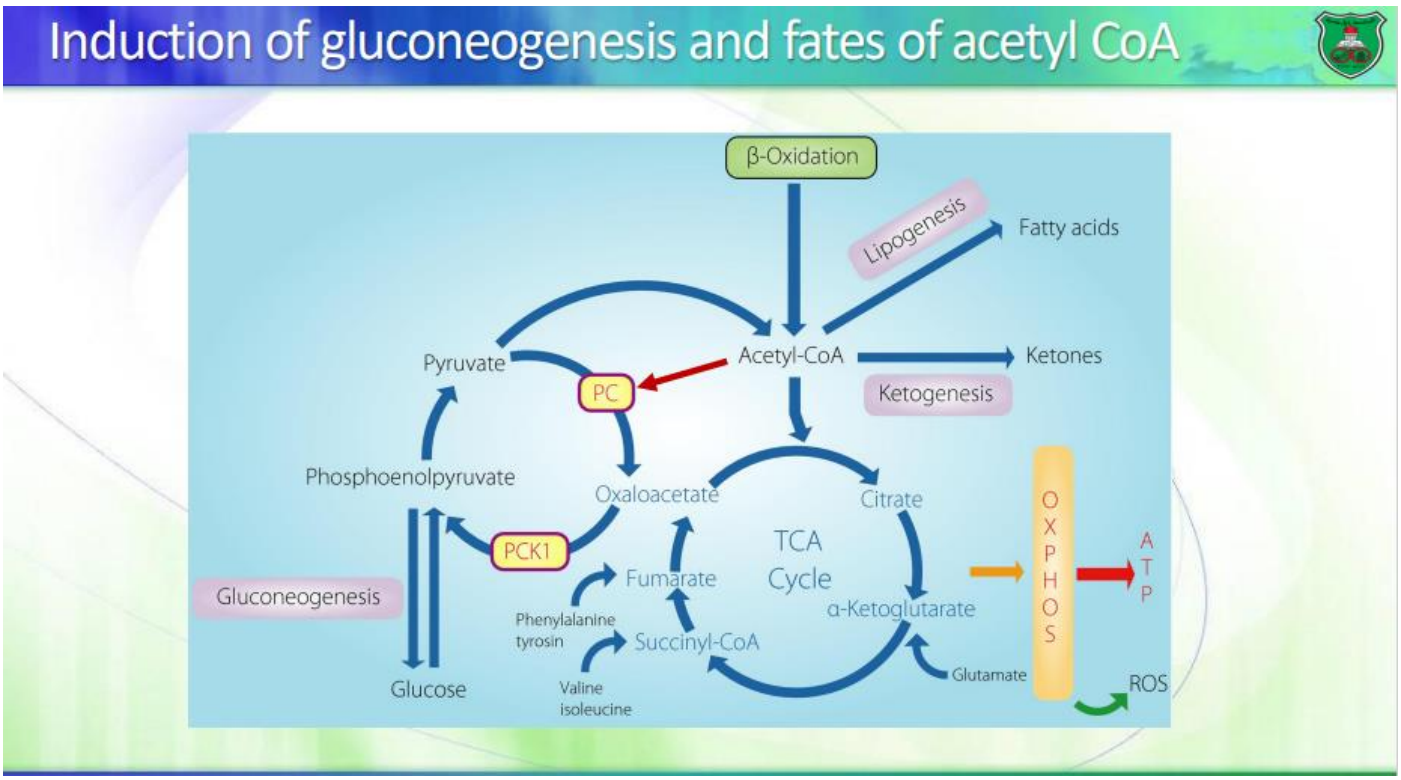
So a lot of ATP is produced.

But remember that the first reaction involves activation of fatty acids (palmitate or palmitic acid is converted into palmitoyl Co that consumes ATP which gets converted to AMP like hydrolyzing 2 ATP molecules, so it is -2 for that reaction).

Why 2 ATP not just one?

Because you convert ATP to AMP without passing through ADP, reducing 2 phosphate groups, so in order to regenerate this ATP from AMP you need 2 phosphate groups.

* The source of CoA is Vitamin B5 (extra information) .



Acetyl CoA has different fates

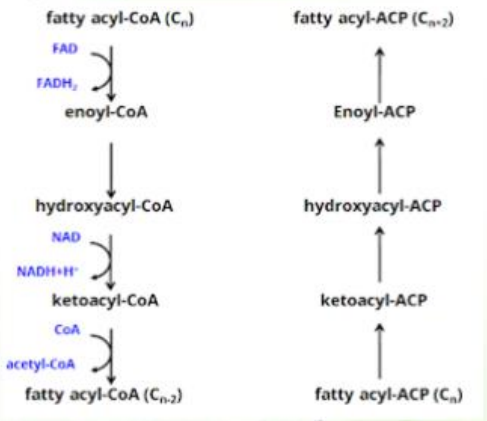
When I have high level of acetyl CoA :

1. I can synthesize fatty acids from it
2. It can be converted to ketone bodies
3. It can enter Krebs cycle

4. It can activate PC (pyruvate carboxylase) which convert pyruvate to OA depending on the body need and the OA goes to Krebs cycle or converted to PEP (phosphoenolpyruvate) then to glucose (gluconeogenesis) .

Synthesis vs. degradation

VARIABLE	SYNTHESIS	DEGRADATION
Greatest flux through pathway	After carbohydrate-rich meal	In starvation
Hormonal state favoring pathway	High insulin/glucagon ratio	Low insulin/glucagon ratio
Major tissue site	Primarily liver	Muscle, liver
Subcellular location	Cytosol	Primarily mitochondria
Carriers of acyl/acetyl groups between mitochondria and cytosol	Citrate (mitochondria to cytosol)	Carnitine (cytosol to mitochondria)
Phosphopantetheine-containing active carriers	Acyl carrier protein domain, coenzyme A	Coenzyme A
Oxidation/reduction coenzymes	NADPH (reduction)	NAD^+, FAD (oxidation)
Two-carbon donor/product	Malonyl CoA: donor of one acetyl group	Acetyl CoA: product of β-oxidation
Activator	Citrate	—
Inhibitor	Palmitoyl CoA (inhibits *acetyl CoA carboxylase*)	Malonyl CoA (inhibits *carnitine palmitoyltransferase-I*)
Product of pathway	Palmitate	Acetyl CoA
Repetitive four-step process	Condensation, reduction dehydration, reduction	Dehydrogenation, hydration dehydrogenation, thiolysis



The table above makes a comparison between the synthesis and degradation of fatty acids , have a look on it (as the doctor said)

Inhibition of CPTI= inhibiting the transport of fatty acids into the mitochondrial matrix.

Dehydrogenation = oxidation

Pay attention to the donor of carbons in synthesis, it is malonyl CoA, while in elongation after synthesis is Acetyl CoA.

as we said before we have 4 sizes of fatty acids chains (short , medium , long , very long) so if I start degradation from long chain it will be medium then short …

each size of these chains has specific dehydrogenase , so there are 4 isozymes of fatty acyl CoA dehydrogenase for SCFA, MCFA, LCFA, and VLCFA.

- **MCAD deficiency** : Medium-chain fatty acyl CoA dehydrogenase (MCAD) deficiency

-Medium chain fatty acids rich in milk , and some infants have deficiency in MCAD so they have deficiency in formation of energy from medium chain fatty acids

-An autosomal-recessive disorder

-Most common inborn error of β-oxidation (1:14,000 births worldwide)

-Higher incidence in Caucasians of Northern European descent

-Decreased ability to oxidize MCFAs (lack of energy)

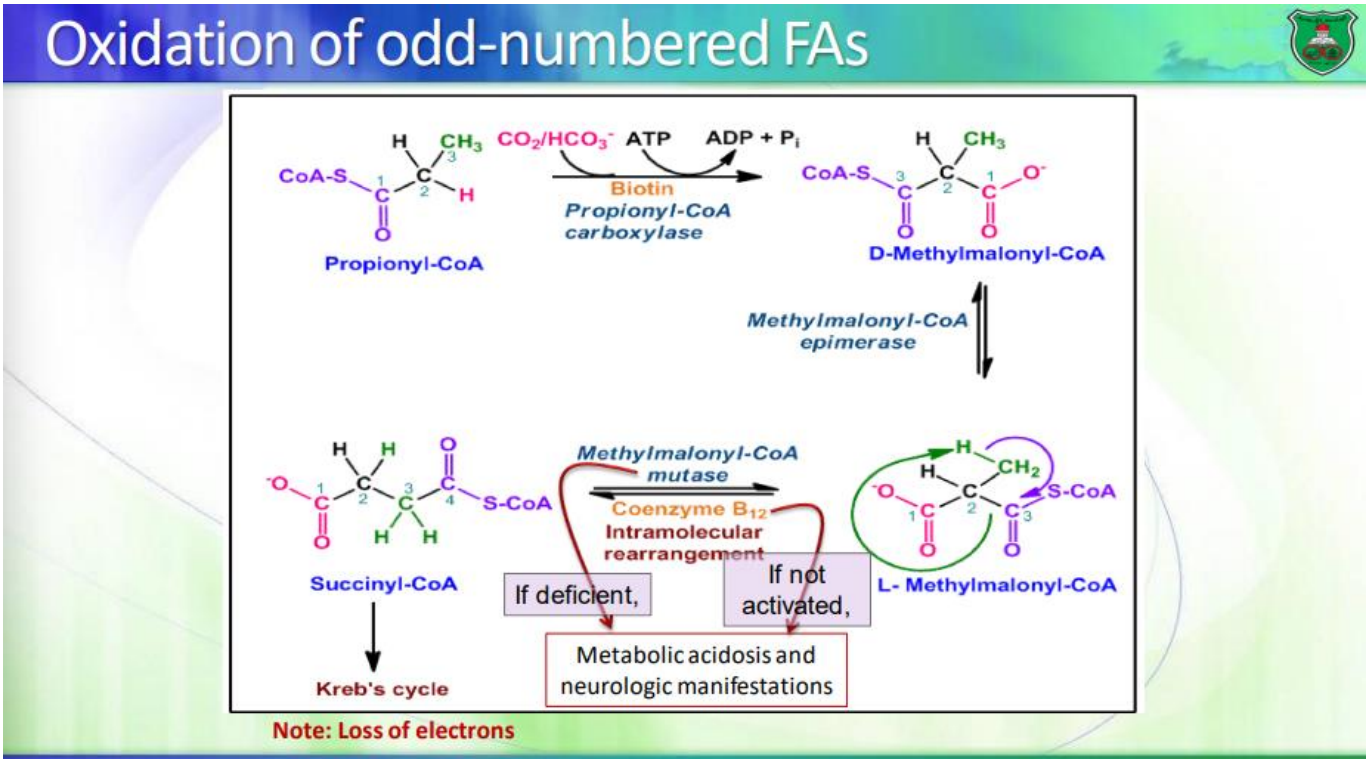
-Severe hypoglycemia and hypoketonemia because the demand on glucose will increase

-Treatment: avoidance of fasting

NOW , sometimes there are some problems facing the oxidation process **(these problems are not diseases)** , but every problem has a solution , and these problems are :

1. Odd-numbered FAs
2. Monounsaturated fatty acid
3. Polyunsaturated fatty acid

let me explain them for you :



imagine that you have a fatty acid chain of 7 carbons , you will break the first acetyl CoA , it will be 5 carbons , break another acetyl CoA , it will become 3 carbons chain which is called propionyl – CoA (look at the figure) .

Then , this chain will be converted to 4 carbon chain which is called D-Methylmalonyl – CoA (D conformation) through an enzyme called propionyl – CoA carboxylase , this enzyme needs ATP , CO_2 and Biotin (B7) , we call this reaction carboxylation (look at the figure) .

After that , we go through 2 isomerization reactions :

1. You have an epimerase which is called (methylmalonyl-CoA epimerase or methylmalonyl-CoA racemase) that changes it to L-conformation , the result is L- methylmalonyl-CoA (look at the figure)

2. Then through an enzyme called methylmalonyl – CoA mutase , L-methylmalonyl-CoA will be converted to succinyl – CoA that proceed in Krebs cycle (look at the figure) , this enzyme needs B12 coenzyme .

In this case , there is loss of electrons , because I did not use the propionyl – CoA in beta oxidation , and the I used the succinyl – CoA in the middle of Krebs cycle (the first steps which produce electrons are skipped)

sometimes , there will be deficiency or inactivation in mutase or B12 , this will lead to accumulation of methylmalonyl CoA (or the propionyl CoA as doctor said) because the reaction will not occur and this will cause metabolic acidosis (because of dependance on ketone bodies) as well as neurological manifestations and nerve injury .

Let's talk about Monounsaturated fatty acids

How do cells handle double bond in fatty acids?

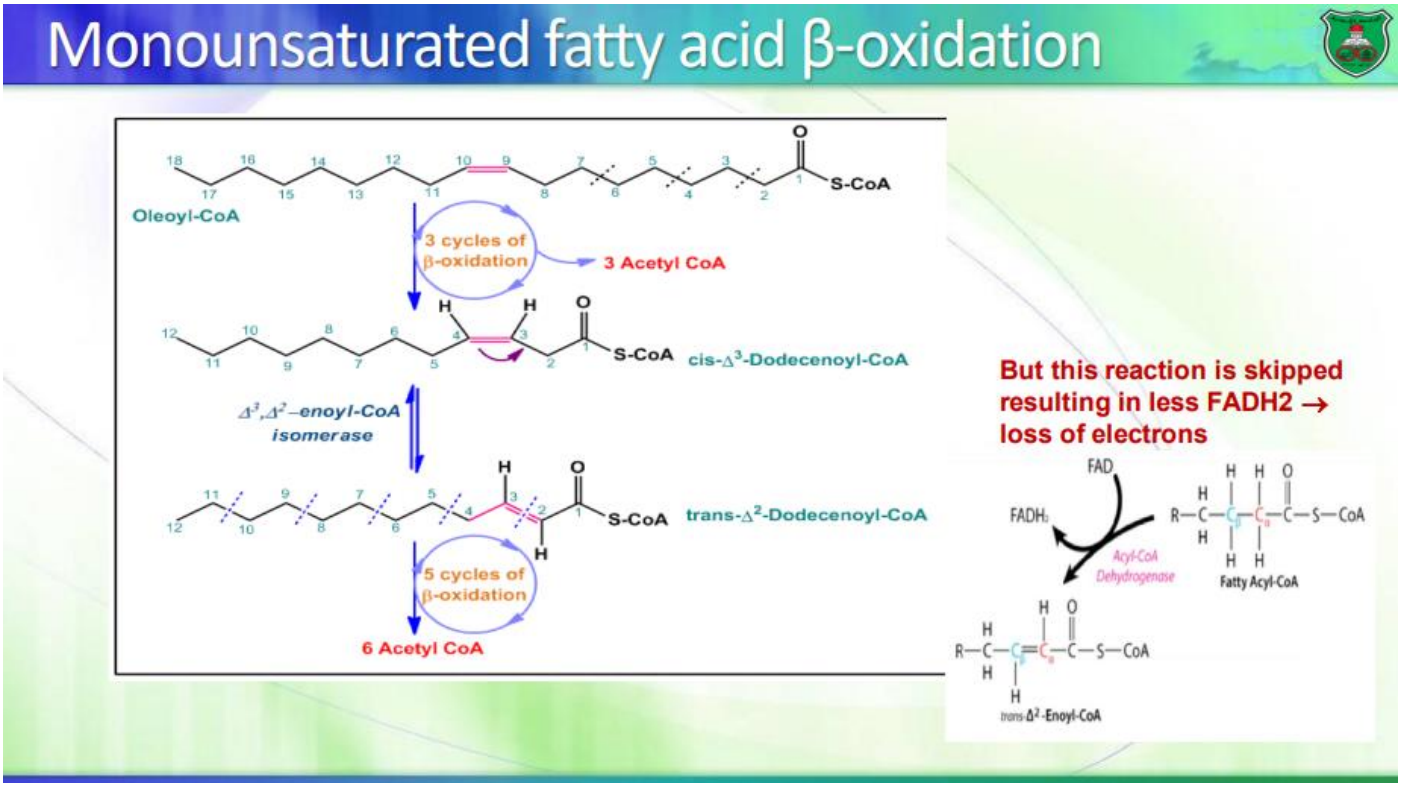
Well, an example is oleic acid:

1. oleic acid undergoes beta oxidation just like any other fatty acid (you have removal of Acetyl CoA one at a time "2 carbons at a time").

2. Until you get near to the double bond, what's important that where this double bond is existing (does it exist at even numbered carbon or an odd numbered carbon), now in this case, it exists in odd numbered carbon that is number 9 (look at the photo below), and down to it a fatty acid with double bond in carbon number 3 (we get it after 3 cycles of beta oxidation that was applied on the original fatty acid which has the double bond on carbon 9).

3. What happens here is that you need an isomerase enzyme, and what this enzyme does that it changes the location of the double bond from cis 3-4 carbons bond to trans 2-3 carbons bond, the result (the last molecule in the photo below) is very similar to the product of the first

reaction of beta oxidation, (remember: the first reaction in the lower right part of the photo below, it is an oxidation reaction of fatty acyl CoA molecule)
creating the double bond, so the result of first reaction of beta oxidation looks exactly like the molecule that result from the isomerization of the odd numbered 3-4 double bond fatty acid). "We don't start with the original compound rather we start with the compound that looks like the product of first reaction in beta oxidation"
4. Since this reaction (first reaction in beta oxidation) results in the production of FADH2 and we skipped this reaction because our compound looks like the product of this reaction, so we have a loss of FADH2 (meaning we loss 1.5 ATP).



How about polyunsaturated fatty acids?

Each polyunsaturated fatty acid has at least 2 double bond one on odd-numbered carbon and another one on even-numbered carbon. The odd numbered is the same thing as oleic acid, but the even numbered double bond oxidation requires extra steps with their enzymes. Let's take linoleic acid as an example:

1. You start with beta oxidation (removing Acetyl CoA).

2. Once we get to the odd-numbered double bond, you need an isomerase enzyme that moves the double bond from carbon number 3-4 to carbon number 2-3 (just like oleic acid).

3. Remember that you have the removal of Acetyl CoA but you have skipped the oxidation reaction of beta oxidation process and loss FADH2.

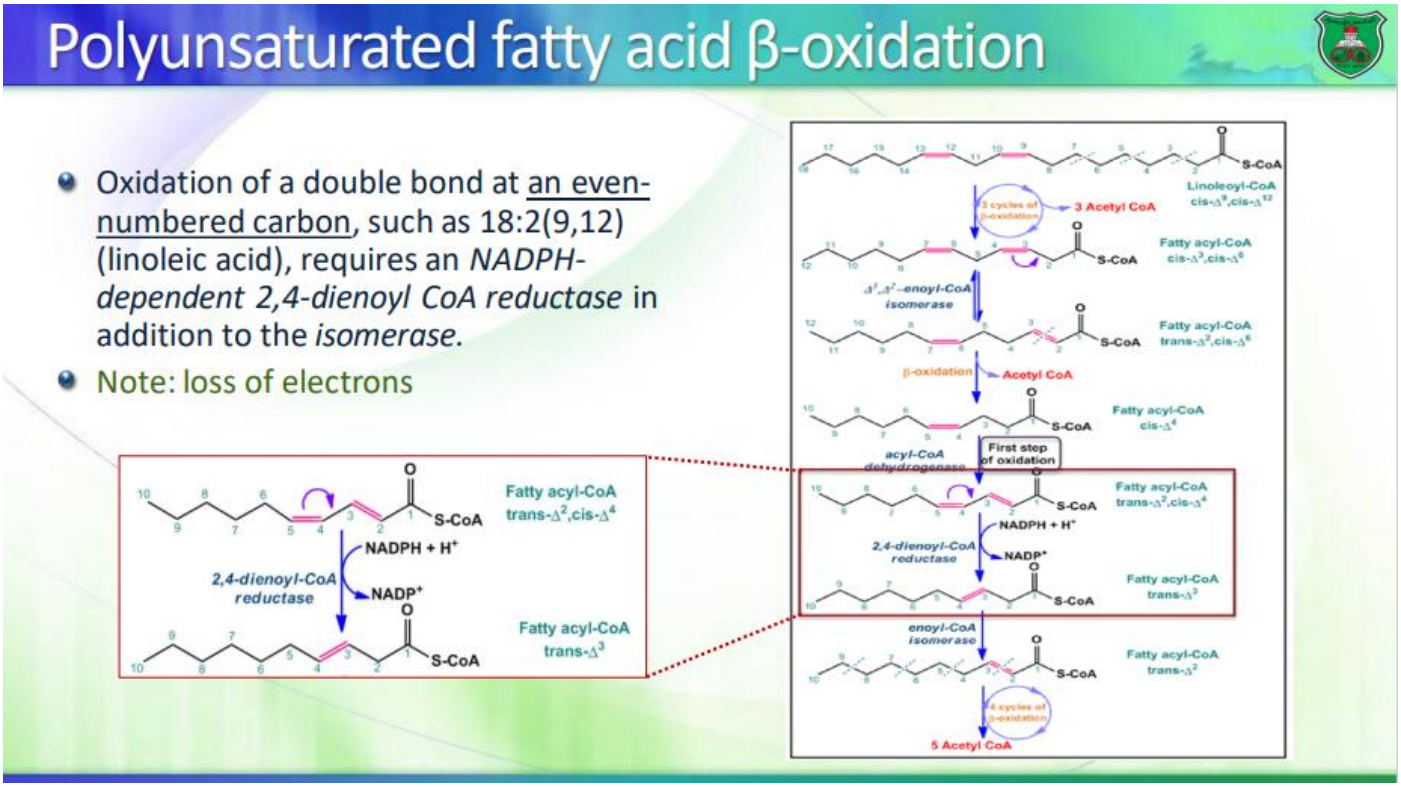
4. Then beta oxidation continues. Once you get to the second double bond (fourth compound at the following photo) you need this additional reaction (and this reaction is catalyzed by dehydrogenase enzyme, by creation of double bond (look at the photo), so you have 2 double bonds, notice their locations.

5. You need a reductase enzyme, what reductase does is it saturate one of them and change the location of the another, it combines these two double bonds into one between carbons 3-4 using NADPH.

6. This is followed by the same isomerase that is needed for oleic acid, so you need this enzyme to move the double bond from carbons 3-4 to 2-3.

7. Again, you can continue with beta oxidation starting from the second reaction not the first because the compound looks like the

product of first reaction of beta oxidation.



*** The doctor said that he doesn't care about the names of the enzymes , but we must know types of reactions that we need in each step .

Now , let`s talk about how cells metabolize very long chain fatty acids (VLCFAs) :

** (Peroxisomes) are needed , beta oxidation of VLCFA takes place in the peroxisomes (exactly like that in the mitochondria) , so we convert VLCFA to long chain fatty acid which will continue in the mitochondria .

1. (Peroxisomes) are needed, what first happens is that you need to activate these fatty acids, just like mitochondrial beta oxidation to

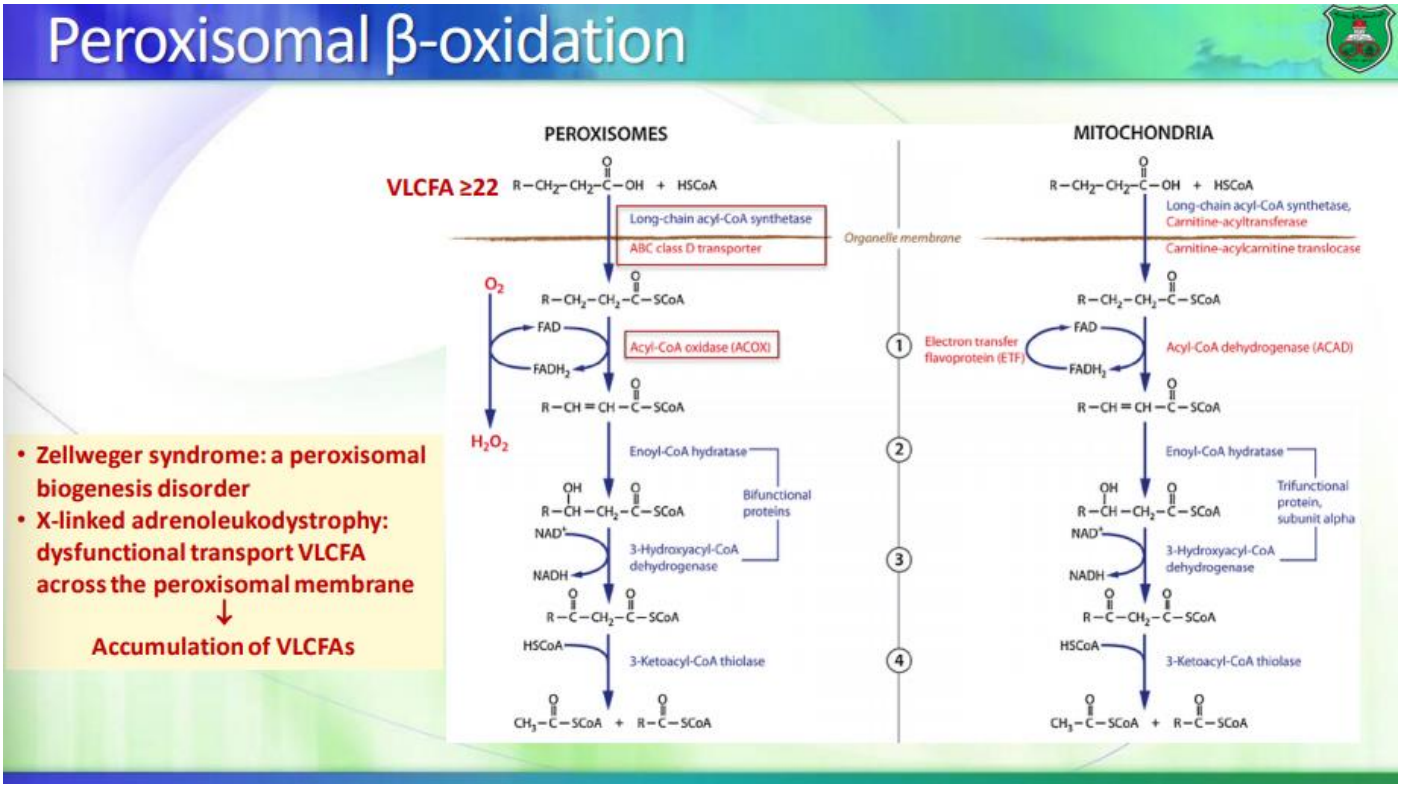
allow fatty acids enter the mitochondria, and for VLCFAs you need activation by attaching Coa to them to allow them to enter the peroxisomes and they need special transporter for that known as ABC class D transporter (different than CPT)

2. Once they are in the peroxisomes they undergo oxidation, it is known as Peroxisomal Beta Oxidation, it's just like the mitochondrial beta oxidation (oxidation, hydration, oxidation and thiolytic cleavage).

3. What happens, is oxidation of fatty acid (formation a double bond just like mitochondrial beta oxidation and you need the electron carrier FAD) look at the photo below, same as mitochondrial beta oxidation but with different enzymes (we use acyl-CoA oxidase (ACOX) in peroxisomal which produces FADH2 that must be regenerated again to FAD), regeneration of FAD is linked to the reduction of molecular oxygen to H202 then to H20 which is catalyzed by catalase

4. The other reactions continue as the mitochondrial beta oxidation, and eventually you will get Acetyl CoA and you will get shorter fatty acid.

5. What happens to the Shortened fatty acids that they get attached to carnitine in Peroxisomes, they leave the Peroxisomes and they get into the mitochondria where you have a continuation of beta oxidation of the fatty acyl CoA, and the entry of Acetyl CoA in Krebs cycle.



*** important note : the FADH2 that produced in peroxisomal oxidation is directly used in " peroxidation " (which is a process to remove hydrogen peroxide) and not for energy , so H_2O_2 is converted to $2H_2O$, and this happens through an enzyme called catalase (the enzyme uses the FADH2) , (only the FADH2 is used , only) .

- There are some pathological conditions that are related to peroxisomal beta oxidation, we will talk about two of them:

1. Zellweger syndrome, it is related to biogenesis of the Peroxisomes (the creation of Peroxisomes in cells), so the very long fatty acids will be excreted without metabolizing

2. X-linked adrenoleukodystrophy: it is related to deficiency or abnormality in the transport of fatty acids into the Peroxisomes and that leads to accumulation of these fatty acids in the blood and tissues

In some cases , we have fatty acids that is branched , so this goes under what we call " peroxisomal alpha oxidation "

-peroxisomal alpha oxidation : Peroxisomal Alpha oxidation is basically the metabolism of chlorophyll, if you eat green leaves there is chlorophyll inside them
The product of breaking down of chlorophyll is phytanic acid (look at its structure in the photo below) it is branched (there is a methyl group branched from the beta carbon), there is an enzyme that is necessary in metabolism of phytanic acid.

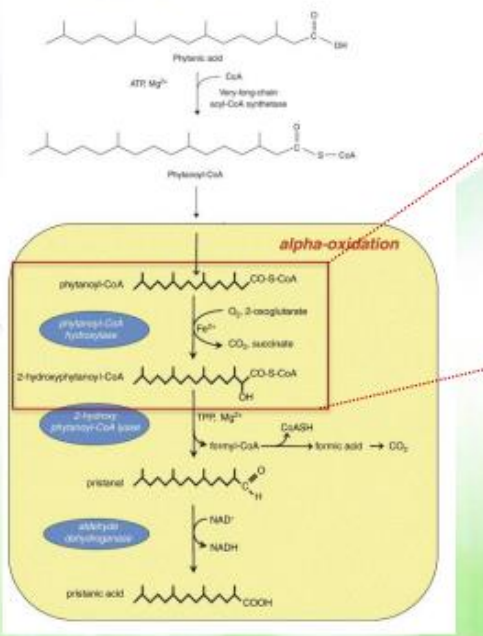
1. Phytanic acid needs to be activated, by attaching a CoA.
2. It gets hydroxylated at Alpha carbon (there is a hydroxylase enzyme that is needed for this reaction).
3. Another reaction that results in the breaking down **between Alpha carbon and the first carbon** (that is why we call it alpha oxidation) and you have the formation of byproduct known as formyl CoA.
4. We have the continuation of breaking down of phytanic acid, until there is another methylated carbon.

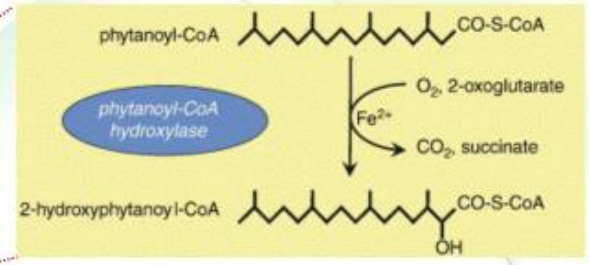
The products of metabolism of phytanic acid are:
1. Formyl acid (Formyl CoA)
2. Methylpropionyl CoA
3. Acetyl CoA
4. Propionyl CoA (it follows the metabolism of odd numbered fatty acids and gets converted to succinyl CoA)

** we call it alpha oxidation because we break exactly before alpha carbon **(between alpha c and the first c)** (releasing **the first carbon** as CO_2) .

** the doctor said what is important to know that hydroxylation happens to alpha carbon and the the products of metabolism of phytanic acid that I mentioned above .

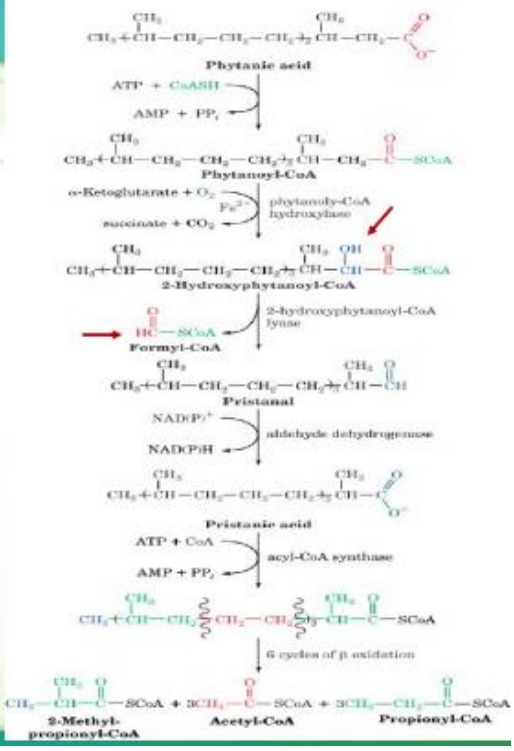
Peroxisomal α-oxidation





Peroxisomal α-oxidation

- Phytanic acid is a breakdown product of Chlorophyl.
- It is activated by CoA, transported into peroxisome, hydroxylated by phytanoyl CoA α-hydroxylase (PhyH), and carbon 1 is released as CO2.
- When fully degraded, it generates formyl-CoA, propionyl-CoA, acetyl-CoA, and 2-methyl-propionyl-CoA from the methyl-end.
- Refsum disease is an autosomal-recessive disorder caused by a deficiency of peroxisomal PhyH.



-we have something that is called “ Omega oxidation “

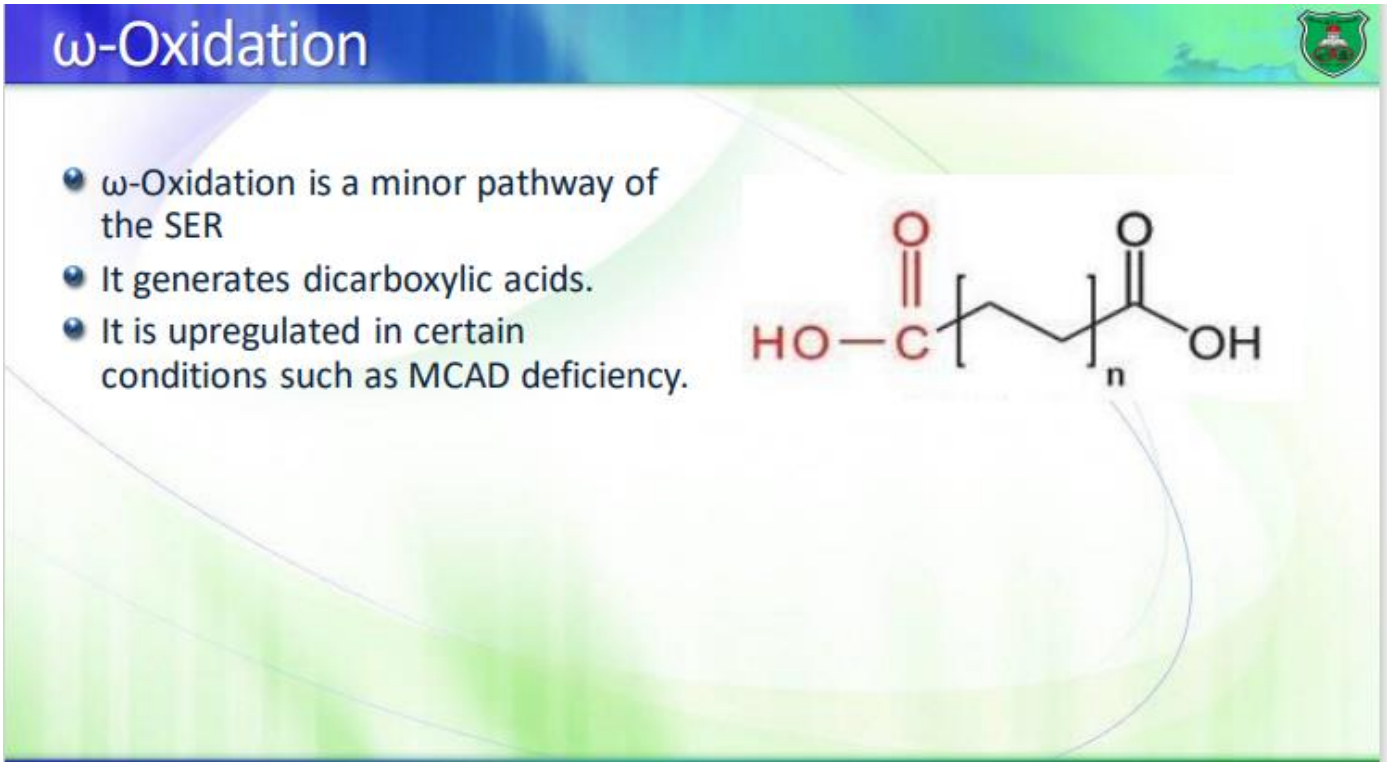
It is related to oxidation that starts from omega carbon which is the very last carbon in the fatty acid chain.

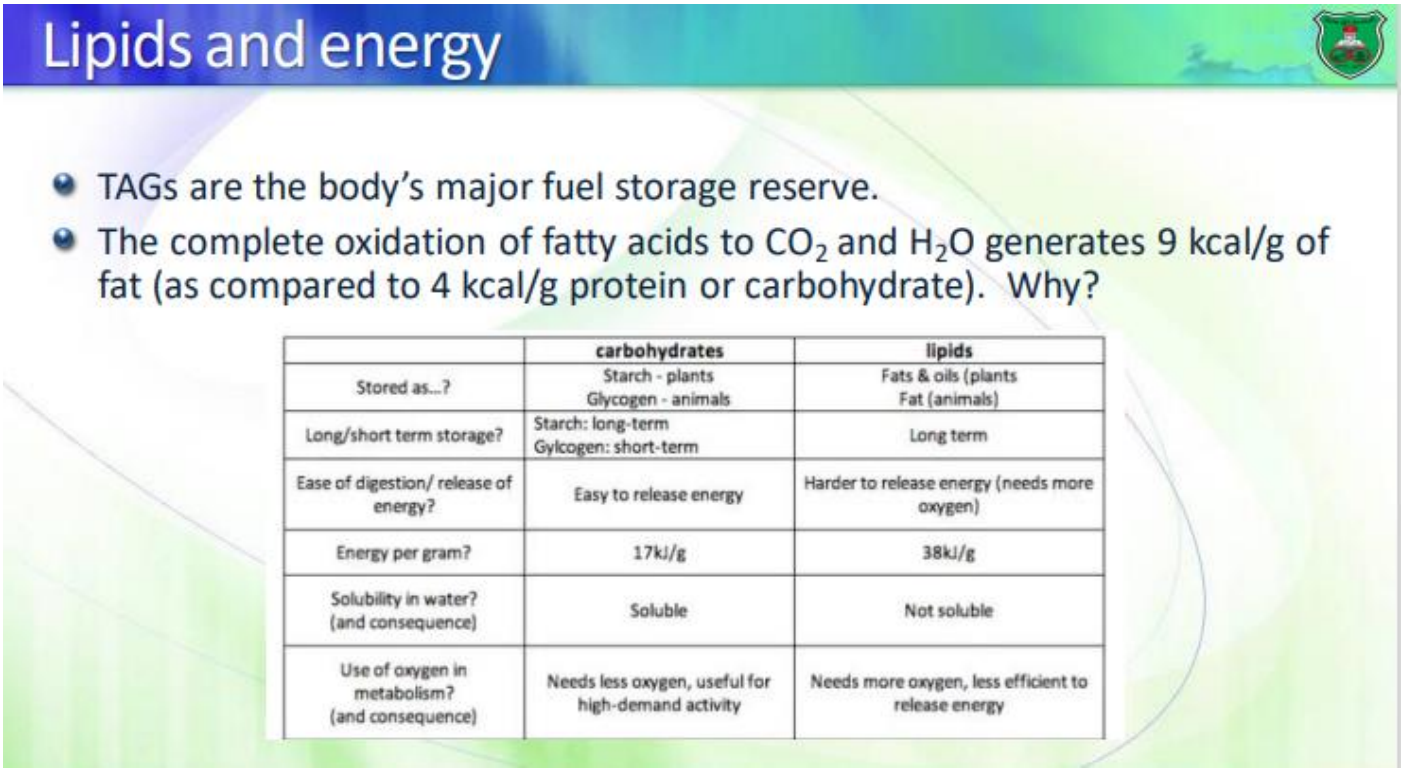
And that's why we say omega 3 omega 6, we are talking about methyl group right here.

It is a minor not a major pathway in the smooth endoplasmic reticulum SER.

What happens is that the methyl group is converted into a carboxylic group, so you have 2 carboxylic groups at this fatty acid molecule (one at either end) , this is why it is called omega oxidation , and maybe then proceed in beta oxidation (as the doctor said)

It is upregulated in conditions like MCAD deficiency (medium chain fatty acyl dehydrogenase deficiency).





About this slide , the doctor said it is just to make comparison between lipids metabolism and carbohydrates metabolism in terms of reactions and amount of energy produced .

- **FINALLY** , " Exercise and sources of energy " :

what do you think the body will choose , lipids (FAs) oxidation or carbohydrates (glucose) oxidation ?

the answer : it is tissue dependent and condition dependent (the condition that the cells are in)

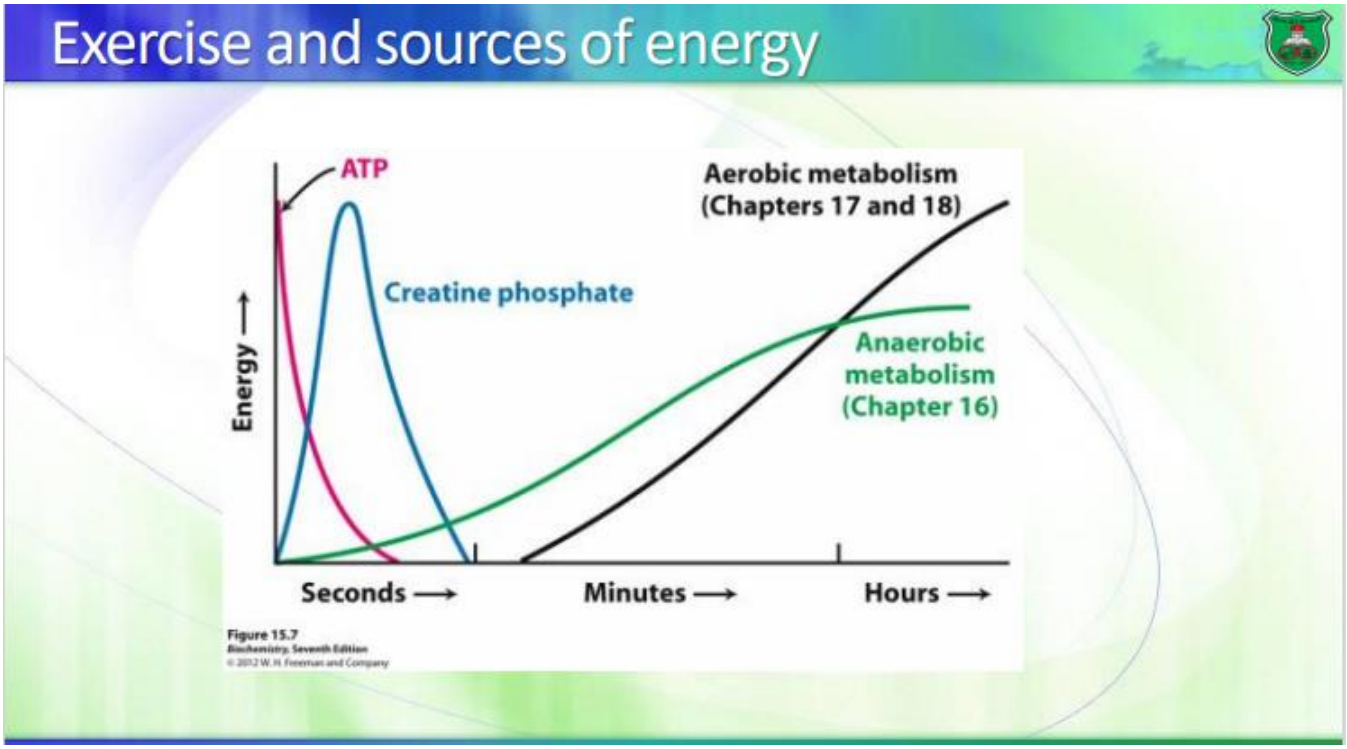
let's talk about skeletal muscles which use FAs metabolism (oxidation) + glucose metabolism .

FA break down depends on the presence of oxygen , if there is no oxygen it goes into anaerobic metabolism which is basically Glucose to lactic acid , so if a Person wants to lose wight he/she has to make aerobic metabolism , so he must make exercise to have enough Oxygen in the body to make oxidation for FA and if he have lack of oxygen in the body or in the cells specifically we will go into anaerobic metabolism as we mentioned .

in Case if you are running, actually muscles don't know how much you are going to run, so the First thing muscles do is using the ATP molecules It has which ends in 5 seconds then it goes to the creatine phosphate , muscles that have this molecule (creatine phosphate) gives phosphate to the ADP to become ATP which is used for muscle movement (mobility) which ends in 30 seconds

*runners depend on ATP in the muscles and on creatine phosphate so they have specific diet depends on creatine phosphate .

after that the body goes to the Anaerobic metabolism to produce some ATP (glycolysis) , and then the body goes to the Aerobic metabolism (needs oxygen) to produce more ATP and the Aerobic metabolism is important for runners to run long distance for long time without exhausting and this is why runners exercise more and more to have more oxygen to make Aerobic metabolism to produce more ATP to run long distance for long time .



THE END

THANK YOU FOR YOUR PATIENCE TO GET HERE ❀ ❀ ❀

NOTES AND CORRECTIONS :

v2:

*** **insulin inhibits the lipases (not activate it) via phosphatase .** page 4 (marked in yellow) , pay attention to this point .

v3:

***point 3 (marked in yellow) , page 26 : **the breaking down happens between alpha carbon and the first carbon**

***note ate the end of the page (marked in yellow) : **we call it alpha oxidation because we break exactly before alpha carbon (between alpha c and the first c) (releasing the first carbon as CO2) .**