DOCTOR 2020 | JU

METABOLISM

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Glycogen Metabolism

In this lecture we are going to study the two pathways related to glycogen which are the synthesis and the degradation of glycogen, but before that we are going to discuss couple of things :

Sources of blood glucose:

1- **Diet:** the first source of glucose**.**
-eating → digestion → absorption→ portal circulation → liver (to check if there is any toxins) → general circulation.
-It is variable between individuals depending on the content of the food we eat (Starch, mono and disaccharides) and the intervals between meals.

2- **Glycogen:** after a carbohydrate rich meal, sugar concentration is increased in the general circulation , insulin is going to be secreted , which will increase the uptake of sugars into the cells**,** now glocose is going to enter glycolysis for the production of energy or it will enter pentose phosphate pathway for the production of pentose sugars and NADPH and the **excess** is going to be directed toward glycogen synthesis, becouse glocose cannot be stored as glocose so we store it as glycogen which will be stored in glycogen granules.

Note: all body cells can synthesize glycogen (in different amounts) but it's stored in large amounts in **liver** and **muscles**.

Now let's say that we didn't have another meal, what will happen is that after two hours of the first meal we will enter in the fasting blood sugar condition and the body need to maintain the glucose level concentration constant in the blood so if it is increased the body will secret insulin, if it is decreased and I'm not going to get it through diet (in the case of fasting), I have another source for it, which is glycogen. So I need to breakdown this glycogen into its subunits or monomers which are glucose residues.

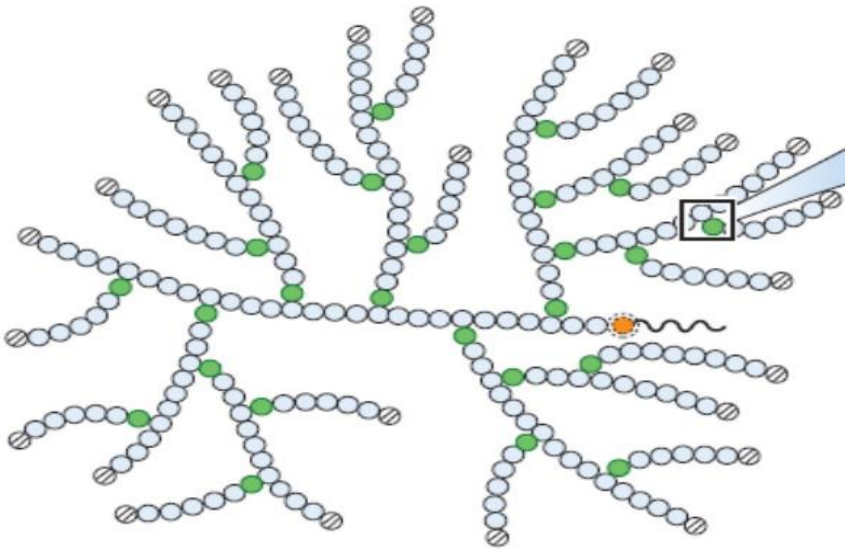
Notes regarding glycogen degredation: 1-it is a **rapid response** (it's pathway is relatively short and the structure of glycogen is highly branched for more efficient degredation) 2-**limited amount** 3-**Important energy source for exercising muscle.**

3- **Gluconeogenesis:** in the case of fasting for a long hours (12-18 hours , depending on how much glycogen is stored in cells) the glycogen will be depleted so now we will get sugar through **Gluco**neogenesis (synthesizing **glucose** from non-carbohydrate precursors)

Notes: 1-it is **Slow in responding** to falling blood glucose levels, even as a pathway it is long (contains 11 steps) 2- It is **sustained synthesis**, so it is important in the case of very long periods of starvation.

Glycogen structure:

- It's a **homo polysaccharide** because it's just made up of glucose, and it's made of a huge number of glucose residues that may reach like hundreds of thousands and the linkage at the branching point **α1,6** whereas the linkages between the sugar residues in the main chain and in the branches other than the branching points are **α1,4.**

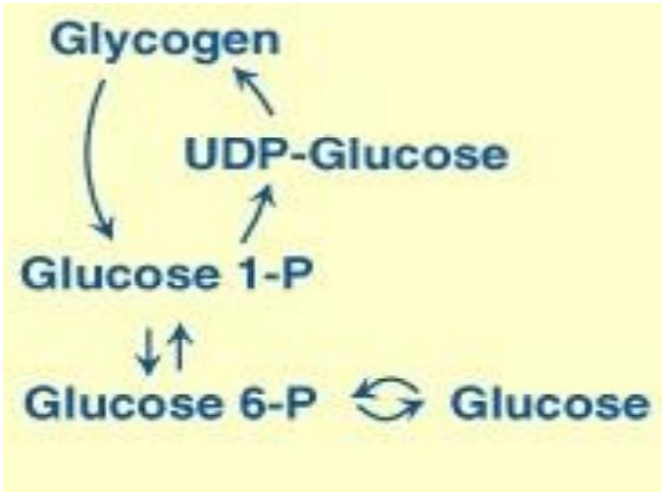


- It's **extensively branched** every 10 residues there is a branch (so many layers of branches that reach like 13 layers) and this what makes it very efficient because we have so many ends that many enzymes can bind to at the same time , so at a unit of time there will be production of a high numbers of residues.

- The ends of the chains are nonreducing because their anomeric carbons (carbon #1) are connected with the previous residue and the carbon that is free at the end is actually #4 rather than #1 , so all the free ends are non-reducing except for the first residue of the main chain(the orange one) because its anomeric carbon is free, but its effect is negligible, **so overall we consider the glycogen to be non-reducing.**

Glycogen synthesis & degradation:

Briefly……..



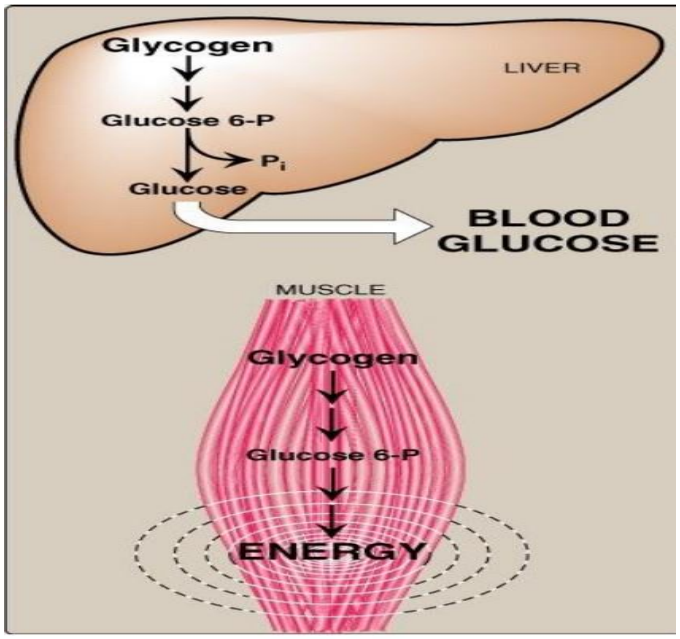
-Glycogen degradation: starts by removing one residue at a time and we start this removal process at the ends (nonreducing ends) these residues are not going to get released as glucose, they are going to get released as **glucose 1-phosphate**, this glucose 1- phosphate is going to get isomerized to **glucose 6-phosphate** then glucose 6-phosphate can be:

1) either dephosphorylated by phasphatases to glucose if this glucose is going to go into blood to maintain the fasting blood sugar.

2) enter glycolysis as (glucose 6-phosphste) to be used for energy production (happens in some cells we will talk about them)

- Glycogen synthesis: in synthesis of glycogen we need glocuse to be in another format to help in regulation between degradation and synthesis ,this format is **UDP-glucose** which is a glucose residue carried by a nucleotide and notice that there many important functions of nucleotides other than being monomers for RNA and in DNA, like being an energy molecule in the case of ATP and another function is carrying molecules during reactions like in our case here also they have other functions that we will talk about in the upcoming lectures.

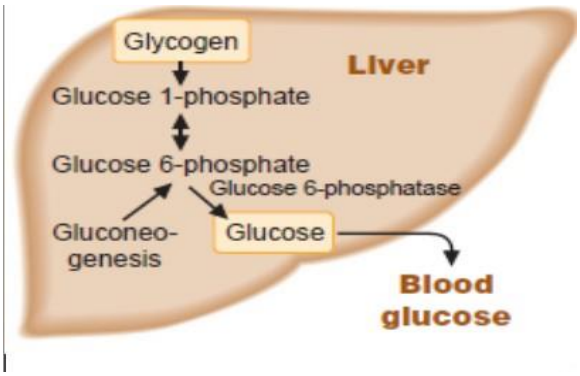
Fates of Glucose that results from glycogen degradation:

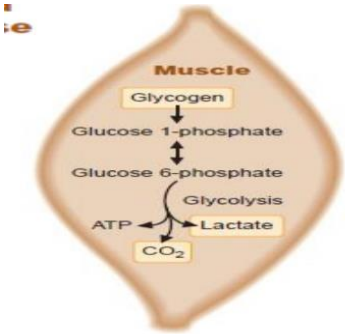


-As we said all body cells can synthesize glycogen (in different amounts) but it's stored in **large amounts** in liver and muscles (also muscles have much more amounts of glycogen stored than in liver) , now what's the difference between muscles and liver?

liver: If this glycogen degradation happens in hepatic cells (liver cells) the produced **glucose 6-phosohate** has to be dephosphorylated by **golucose 6-phasphatase** to **glucose** that is going to get released into the bloodstream to **1-maintain fasting blood sugar levels and 2-to supply cells that are exclusively dependant on glucose** like brain, RBCs, adrenal medulla, and remember here we are talking about glycogen degradation so we are still in the short term fasting conditions (haven't exceeded the 12-18 hours that we talked about earlier)

Muscles: in the muscle this glycogen -which is larger in amount than in the liver- is going to get degraded producing glucose 6-phosphate which is going to be trapped because it doesn't have the enzyme golucose 6-phasphatase so it stops here, and this glucose 6-p can't exit out of the cell because there is no transporter for it and the glucose transports can't transport it because these molecules now have a negatively charged phosphate group so the molecules are different from glucose, **so glucose 6-phosphate is going to enter glycolysis for energy production , unlike liver.**



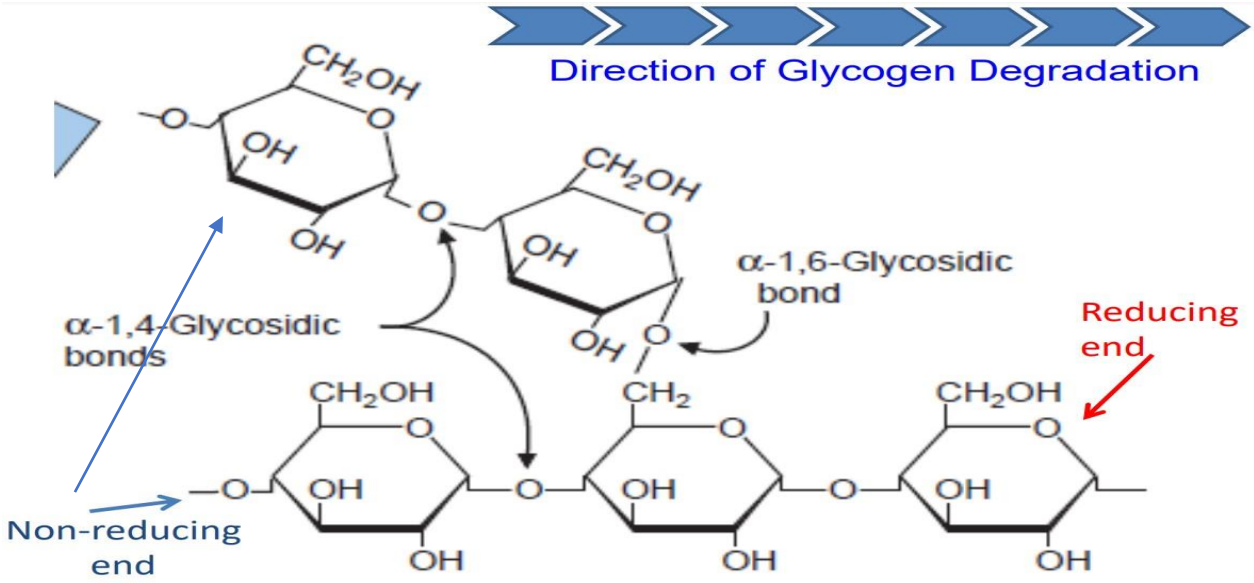


Note: during fasting glycogen stores in liver are depleted faster than muscles and that's because:

1- liver is responsible for supplying blood stream (maintaining fasting blood sugar levels) and supplying glucose dependent tissues where as muscles only use it for itself not for other tissues.
2- the amount of glycogen stored in liver is smaller than the amount in muscle.

- Liver glycogen stores increase during the well-fed state and are depleted during fasting
- Muscle glycogen is not affected by short periods of fasting (a few days) and is only moderately decreased in prolonged fasting (weeks).

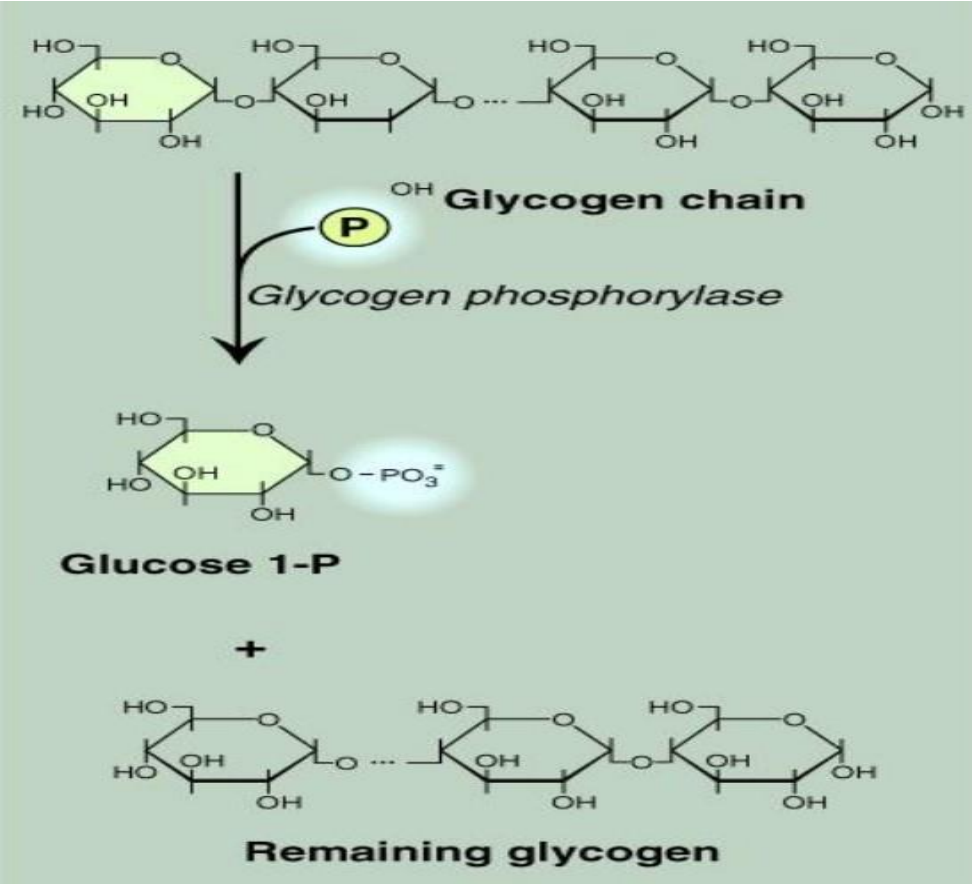
Degradation of glycogen (Glycogenolysis):



-In this figure we can see that degradation starts from the non reducing ends of the main chain as well as the branches (the blue arrows), so **it will go from non-reducing**

ends towards the reducing end or towards the beginning of the branch (in the case of branches.)

-Now we will go more in depth about this pathway :



1. An enzyme (**Glycogen phosphorylase cleaves α1,4 linkge**) removes the non-reducing end and phosphorylates it (it adds inorganic phosphate so it's not a kinase) , resulting in release of **glucose 1-phosphate** and a **glycogen molecule (-1 glucose)** and this enzyme proceeds until we reach the (limit dextrin)

   Note: Limit dextrin is the point where glycogen phosphorylase stops , and it is **4** glucose molecules away from the branching**.**

2. Another enzyme (**debranching enzyme**) would take it from here, this enzyme has two functions:

• A **transferase enzyme function**. • And (**α1-6) linkage cleavage** enzyme function (α1-6 glucosidase)

The transferase enzyme function will cut 3 of the glucose residues from the branch and attach it to the main chain and one glucose residue will remain where the branching occurred.

3. This remaining glucose residue in which the branching happened is linked via an α1-6 linkage; so the glucose phosphorylase can't cleave this bond , and it is here where the (α1-6 glucosidase) part is needed , it cleaves the bond and releases the last glucose residue of the limit dextrin so now we have a **straight chain**.

4. The glycogen phosphorylase will continue its function of degrading the glycogen until another limit dextrin occurs , then the same process happens as described above so is alternation between the two enzymes **Glycogen phosphorylase** and **debranching enzyme**.

5. Lastly the enzyme **phosphoglucomutase** converts **glucose 1-phosphate** to **glucose 6-phosphate** where in muscle it will enter glycolysis to produce energy and in liver the phosphate can be removed by **glucose 6- phasphatase** and released into the blood stream.

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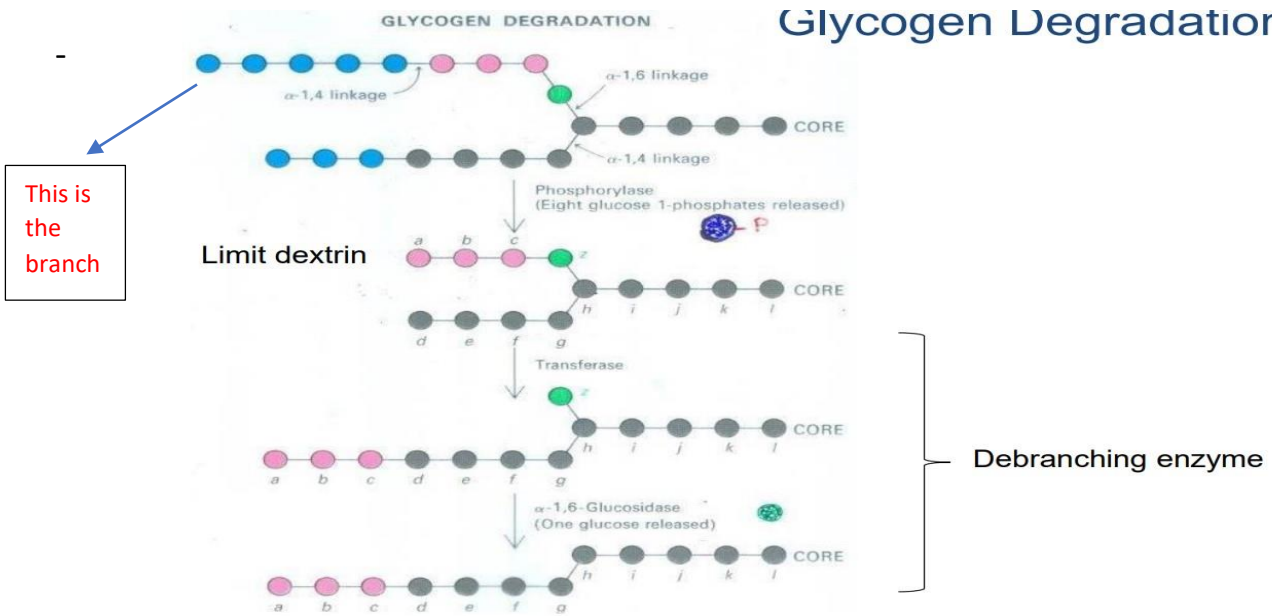


Lysosomal degradation of glycogen: the pathway we discussed is considered the main pathway, however there is a minor pathway in which glycogen can be degraded inside the lysosomes of the cells , this small amount constitutes only 1-3% of glycogen that is present, the enzyme that's present inside the lysosome is called α**(1-4) glucosidase (acid maltase)** acid because it works in the acidic environment of the lysosome and maltase because it cuts at α(1-4) between glucose residues just like maltase, but the purpose of this pathway is unknown.

Although it degrades only 1-3% (small amount) of glycogen of the cell , deficiency of this enzyme causes accumulation of glycogen in vacuoles in the lysosomes (Type II: Pompe disease)

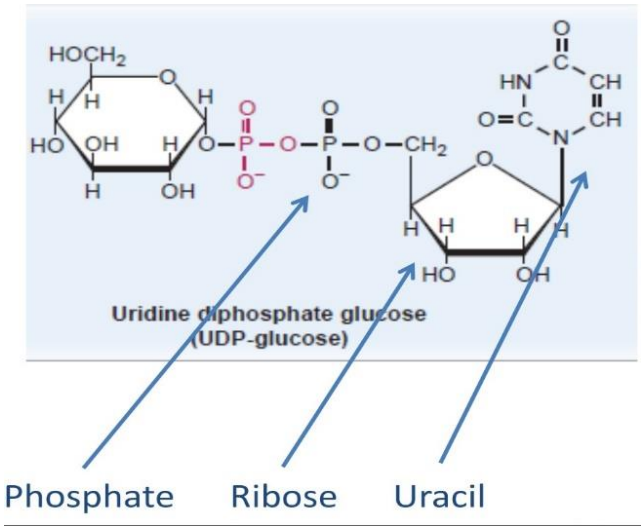
Glycogen synthesis (Glycogenesis):

- now we are in the well-fed stat,there will be large amounts of Glucose/sugar inside the cells transported by the transporters under the effect of insulin, large portion of this large concentration of glucose is going to get stored in the form of glycogen.

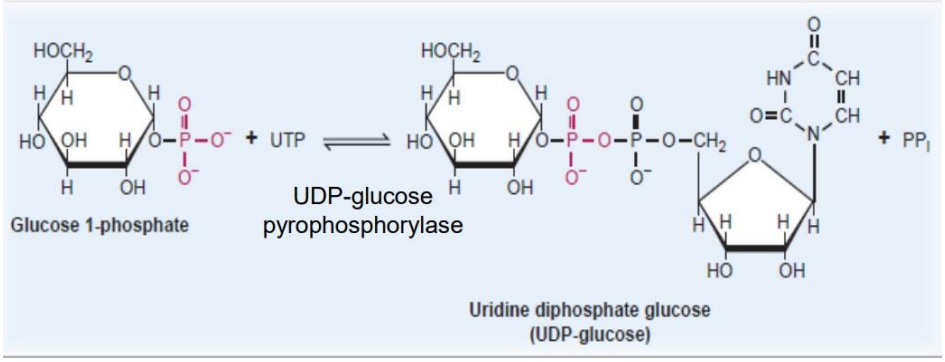
-it is an **anabolic** pathway so it needs energy

- Glycogen is synthesized by adding glucose one by one, **UDP-Glucose** is the active donor of glucose units

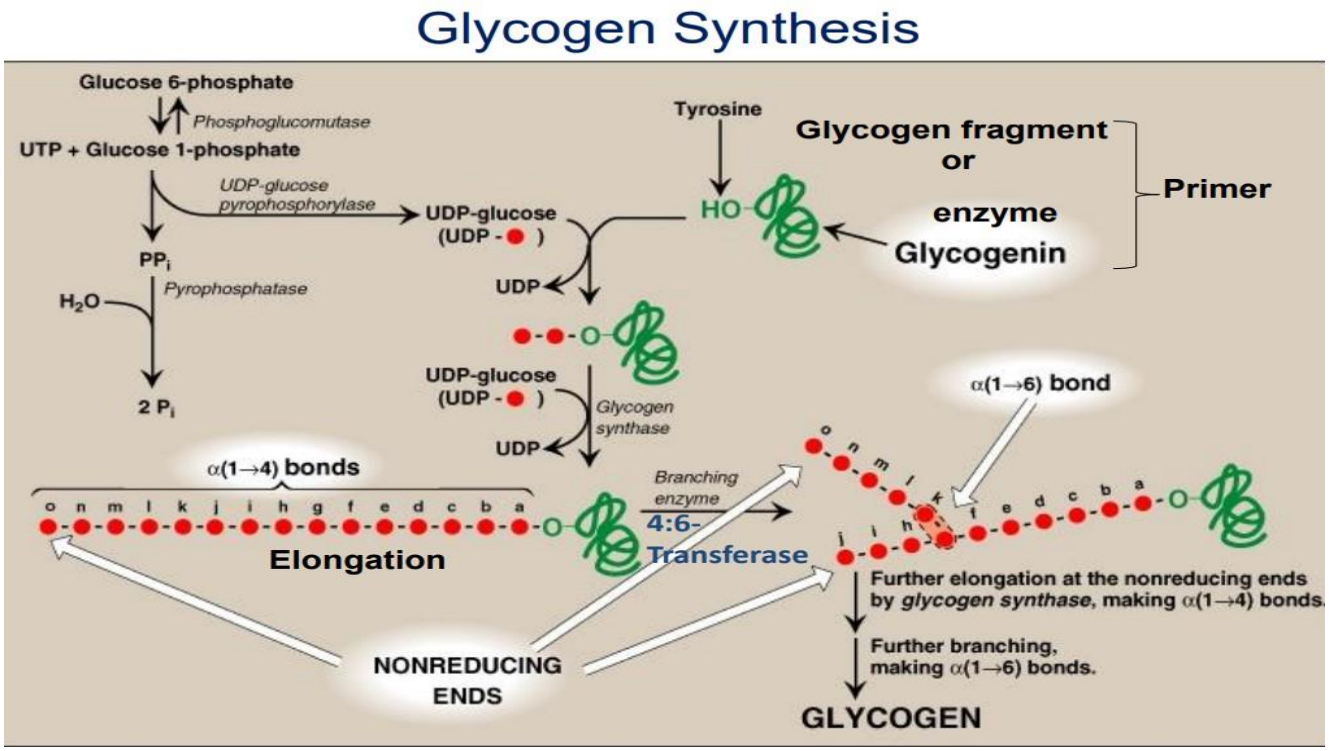
-**UDP-glucose** consists of: **glucose sugar**, **uracil nitrogenous base**, a **ribose sugar** and **2 phosphate groups**



-How does this UDP-Glucose form? It's going to form by interaction between **glucose 1-phosphate** (has one phosphate) and **UTP** molecule (has three phosphates), so in total we have 4 phosphates, the phosphate on the glucose will stay on carbon #1 and two phosphates of the UTP will be releasesd as pyrophosphate so now we will have the formation of UDP-glucose, then pyrophosphate will undergo hydrolysis reaction releasing 2 inorganic phosphates.



- The name of enzyme that catalyzes this reaction is (**UDP-glucose pyrophosphorylase**),and this reaction anabolic pathway needs enery that is supplied by UTP.



-First thing, we know that we are now under well-fed conditions so we have high concentration of glucose inside the cell and this glucose will get phosphorylated to glucose 6-phosphate which can enter into glycolysis or pentose phosphate pathway or it can be used for glycogen synthesis.

- **glucose 6-phosphate** has to be **isomerised** into **glucose 1-phosphate** by the activity of the enzyme **phosphoglucomutase** then g1p will be attached to UTP producing UDP-glucose. Now we have the building block for the synthesis of glycogen which is (UDP-Glucose)

-One thing to note is that we can't build the glycogen molecule straight away , we need some kind of a frame or a base to start adding UDP-glucose molecules on , and it could be either a **small glycogen fragment or a glycogenin molecule (a protein) to act as a primer or a reference**.

Note: Glycogenin is a molecule which contains **Tyrosine amino acid**, tyrosine has OH group on its side chain, so it can interact through the oxygen of this OH group with incoming UDP-Glucose, UDP-Glucose is going to lose the UDP molecule and just the glucose will get attached.

Glycogen synthesis steps:

1. The enzyme **Glycogen synthase** catalyzes the addition of a UDP-glucose molecule to the primer (UDP is released and only glucose is attached) then another UDP-glucose is added to the glucose added earlier and this process is repeated till we get a large main glycogen chain connected via α(1-4) glycosidic linkage (This phase is called the **Elongation phase**)
2. The second **Branching phase** starts (as glycogen is a branched molecule) and another enzyme called **4-6 transferase (also called Branching enzyme)** which catalyze the formation of α(1-6) linkages at the branching points by cutting part of the long chain for example between (J residue and K residue) then transferring it to residue G and attaching it by α(1-6) , then glycogen synthase acts again to elongate the branching chain and the main chain again.

***Those two steps are repeated many times because glycogen is highly branched so it is alternating cycles between the two enzymes.**

- notice that glycogen synthesis & degradation contain few steps.

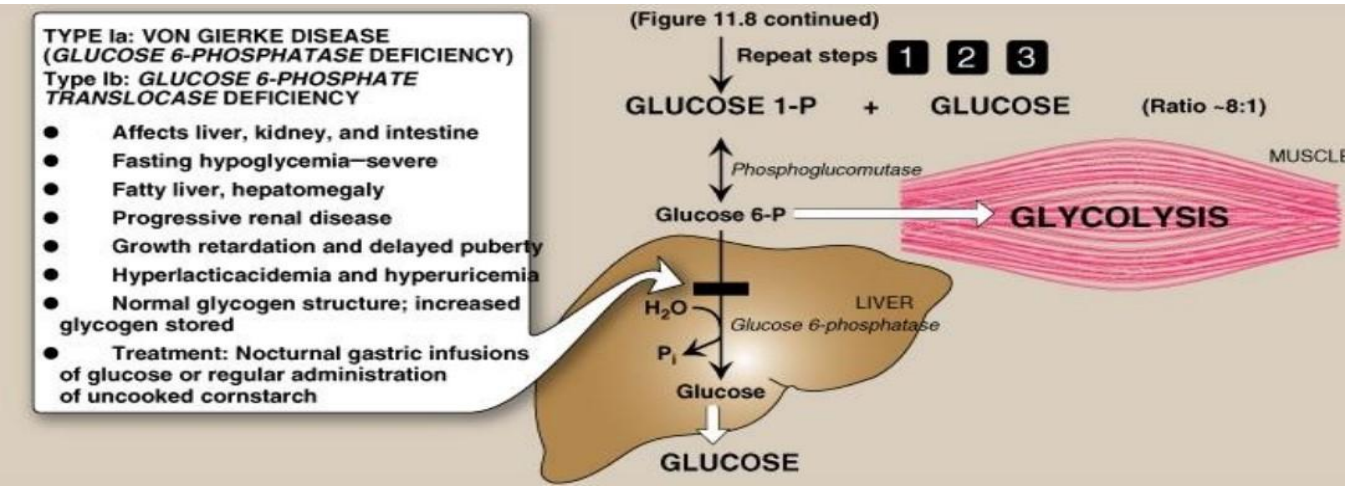
Glycogen Storage Diseases:

- Let's discuss some clinical applications on glycogen metabolism, we'll take a group of glycogen storage diseases, these are **Genetic diseases**.

- Defect in an enzyme required for synthesis or degradation of glycogen, whenever there is a problem in the **synthateic pathway** there would be production of **abnormal** glycogen which will accumulate inside the cells, where as if we have a problem in the **degradative pathway** there would be accumulation of **normal** glycogen which is a big problem because glycogen is polysaccharide so it is a big molecule.

- some of them might be severe to the point of causing death in early infancy and others might be mild depending on the enzyme deficiency whether it affected some tissues or all tissues because sometimes we have many different **isoform** of an enzyme so thay perform the same function between different tissues but have minor differences in the primary sequence that gives them something specific in that tissue so sometimes the enzyme will be abnormal only in one tissue and in all tissues.

1. Glucose-6-phosphatase deficiency (von Gierke disease) (glycogen storage disease type 1)



What happens in this disease?

-Conversion of glucose 6-phosphate into glucose is affected because of the deficiency of the enzyme (**glucose 6-phosphatse**). This reaction happens during glycogen breakdown in the liver (the main source of blood sugar) rather than in muscles because the gene encoding for this protein is inactive in normal conditions in muscle cells.

-We're going to reach to the point that this glucose 6-phosphate can't exit the liver and enter the blood stream, and the low sugar concentration (**sever hypoglycemia**) in the blood signals hepatocytes to break down more glycogen as a compensatory mechanism but the problem here is that glucose 6-P can't exit the liver and this causes **hepatomegaly** also the cell will use this large amount of sugars to synthesize more and more fat causing **fat on liver (fatty liver)**.

-Affects the liver, kidney and intestine.
-causes Severe fasting hypoglycemia.
-Hepatomegaly (enlarged liver), fatty liver.
-causes Progressive renal disease.
- causes Growth and mental retardation because some cells that exclusively depend on glucose -like brain- will be affected, and this is a genetic disease so it will affect the individual since his birth.
-Glycogen structure is normal.

2. McArdle syndrome, Muscle glycogen phosphorylase deficiency (Glycogen storage disease type V)

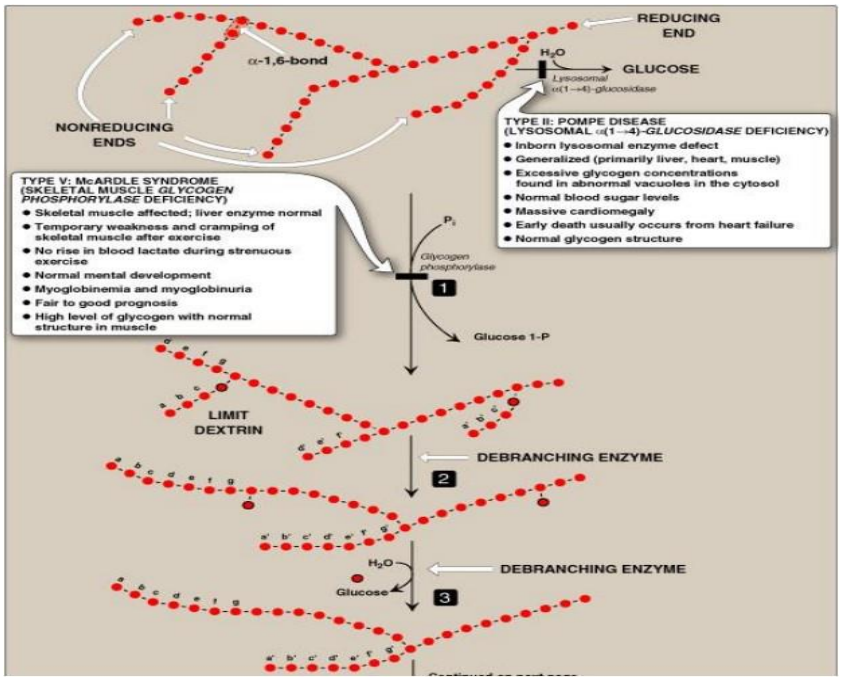
- it affects glycogen phosphorylase **in muscles only**, this enzyme participate in degradation of glycogen.
So what will happen?

- There will be weakness and cramping of muscles because there will be no enough fast source of energy to provide these muscles.
- Anaerobic respiration will also be affected so no increase in lactate production during exercise, because there is no glucose to make pyruvate.

3. Pompe disease, deficiency of lysosomal α(1→4) glucosidase (Glycogen storage disease type II)

- Degradation of glycogen in lysosomes is inhibited (3% of glycogen is degraded in lysosomes), causes excessive glycogen in abnormal vacuoles in the lysosomes.
-mainly affects very active cells like **liver**, **heart** and **muscles** because thay need large amounts of energy so they need this 3%, so for example heart cells will try to **compensate** for the lost energy so they will enlarge in size and this is what is called

cardiomegaly (تضخم في عضلة القلب) and at somepoint it is going to fail causing death, usually happens among elderly but also can happen in young people.
- Normal blood sugar (because the major pathway is intact(سليم)).



Energetics of these pathways:

Glycogen synthesis starting from glucose:

Glucose + ATP ⟶ Glucose 6-phosphate + ADP

Glucose 6-phosphate ⇌ Glucose 1-phosphate

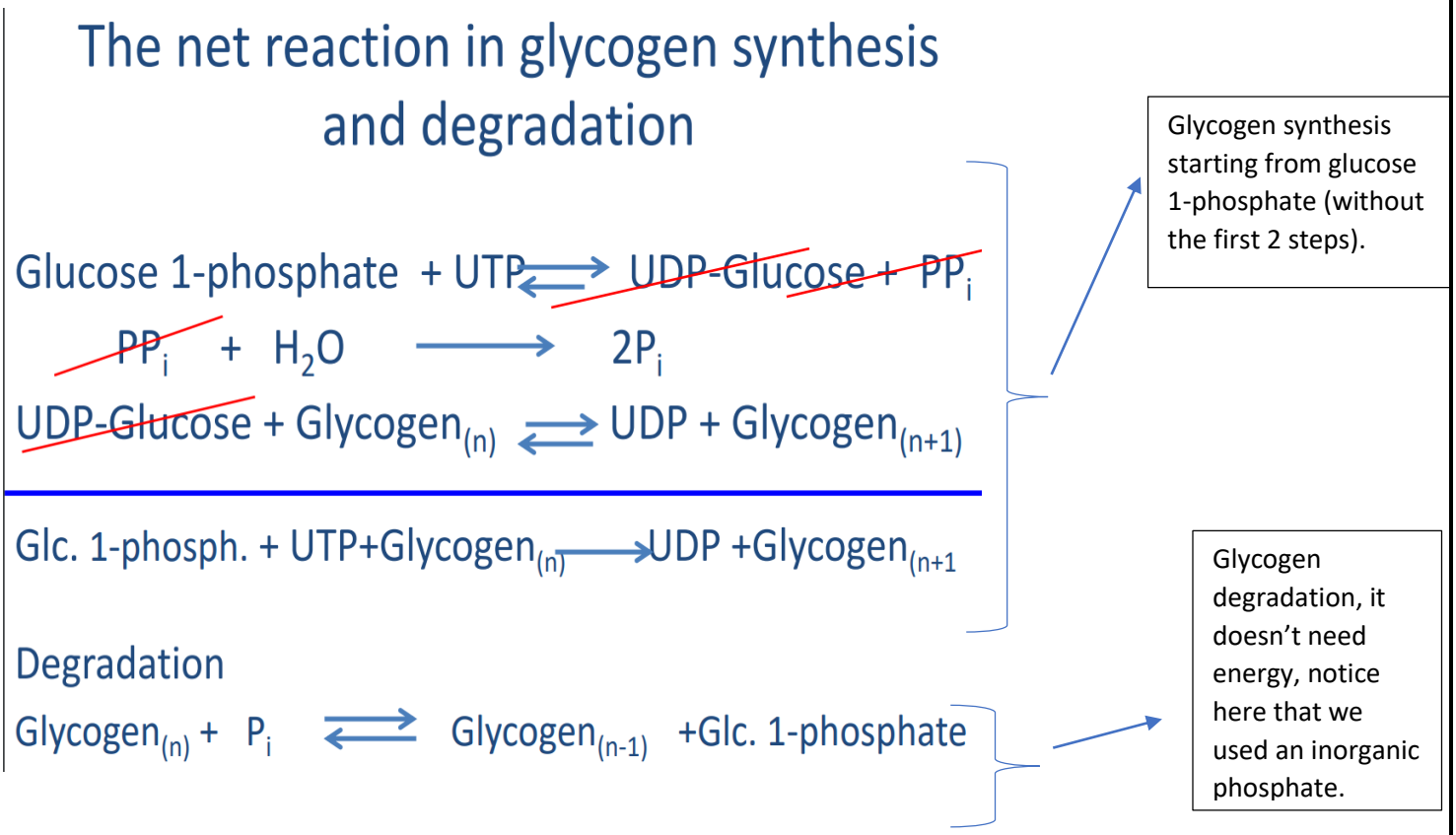
Glucose 1-phosphate + UTP ⇌ UDP-Glucose + PP_i

PP_i + H_2O ⟶ $2P_i$

UDP-Glucose + $Glycogen_{(n)}$ ⟶ UDP + $Glycogen_{(n+1)}$

Glc. + ATP+ UTP+ $Glycogen_{(n)}$ ⟶ ADP + UDP +$Glycogen_{(n+1}$

- **so for every one glucose added 1 ATP and 1 UTP are used** (important), and glycogen was of (n) residues and became of (n+1) residues.



-This slide is just to show you that that the net reaction of the synthesis and the net of the degradation are almost the opposite.

The end