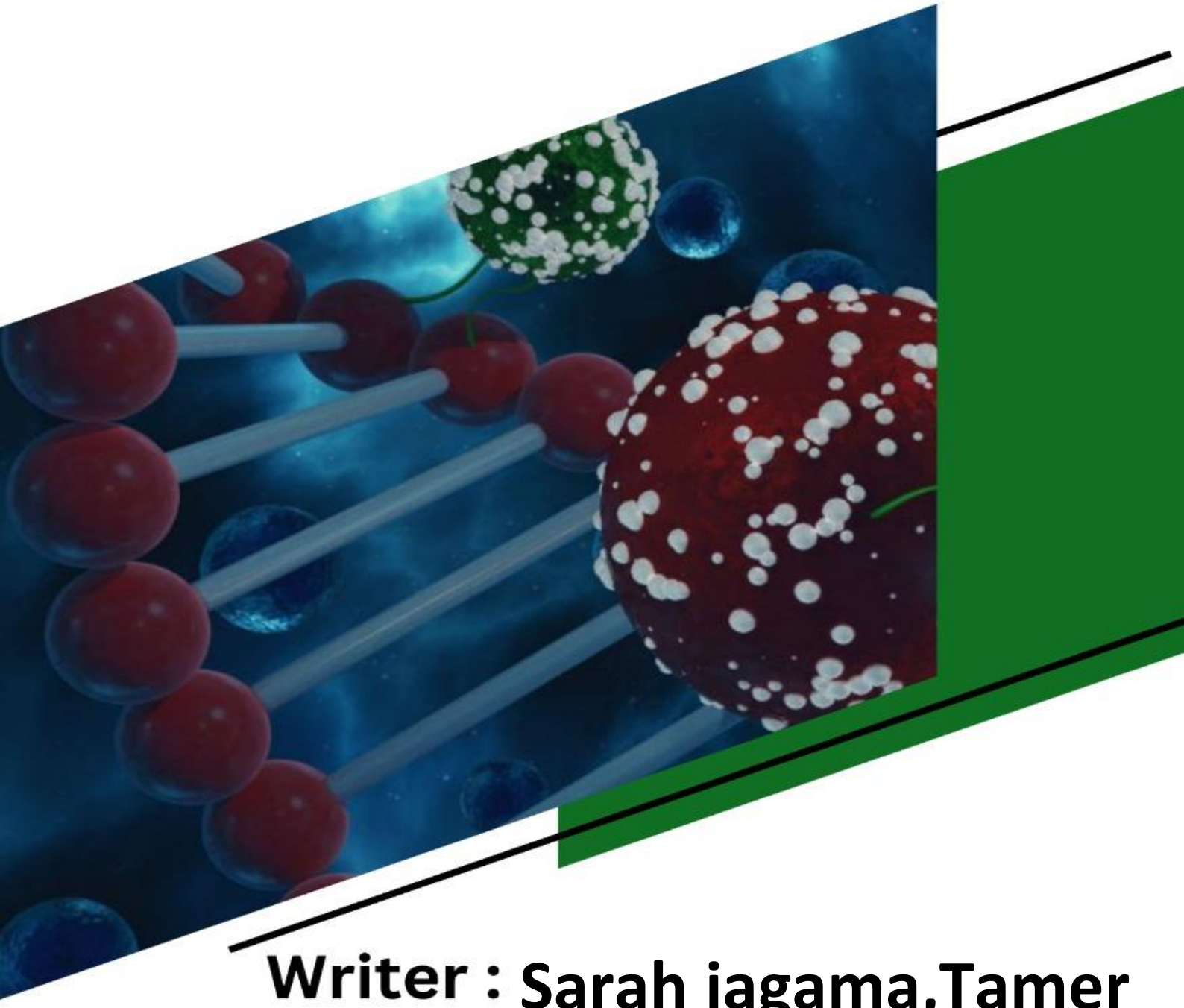
Doctor 021

METABOLISM

Sheet no. 13



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GLYCOGEN METABOLISM

In this lecture we will start talking about glycogen metabolism (synthesis and degradation of glycogen) before we start let's talk about source of glucose in blood.

Okay why we need glucose in blood stream?

Because some tissues are glucose dependent such as brain and RBCs and medulla, the second reason is maintaining osmotic pressure.

- Sources of Blood Glucose

-Diet

Starch, mono and disaccharides, glucose

Sporadic, depend on diet

-Gluconeogenesis

(Synthesis of glucose from non-carbohydrate sources)

-Sustained synthesis

-Slow in responding to falling blood glucose level

-Glycogen

Storage form of glucose

(Glycogen stores last for 12 to 18 hours)

Rapid response

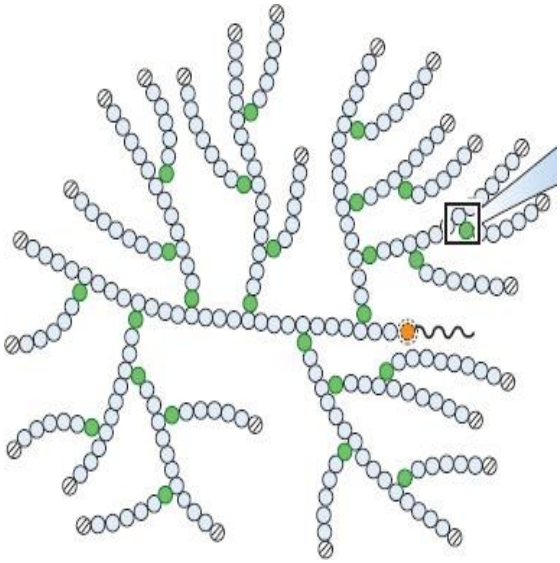
Limited amount

Important energy source for exercising muscle

As we all know when glucose reaches blood stream it will leads to secret insulin by liver, which leads to increase uptake of glucose by cells, part of the sugar will undergo glycolysis and other pathways, excess of glucose will be stored as glycogen once there is no supply of sugar from diet we will break it down into glucose in a quick response.

-Glycogen Structure

-extensively branched homopolysaccharide



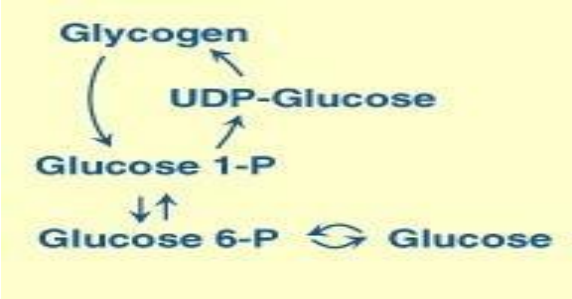
-one molecule consist of hundreds of thousands of glucose units

Note: there are two types of bonds between glucose in glycogen, A (1,4) at main chain and A (1,6) at branches

Why the branches are important? As we all know the first reason is increase solubility, the second one Because we have more ends, so we have more non-reducing glucose lead to more glucose residue which makes degradation of glycogen more rapid

Now let's start talking about glycogen metabolism

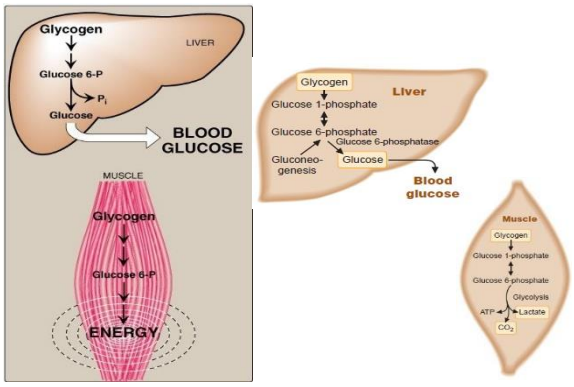
we have two pathways (synthesis and degradation) only one of them running (the two pathways cannot work at the same time to prevent wasting energy)



as we notice from the picture, we need UDP-glucose to synthesis glycogen, and the glucose1-p is result from glycogen degradation, we can distinguish between two pathways through the presence of UDP-glucose

as we all know all of cells can store glycogen, but the largest storage is in muscles and liver (the highest amount in muscles)

-In normal human bodies there are approximately 500 gram of glycogen around 400g of them in muscle cells



-the mechanism of glycogen degradation to reach the blood stream (in the liver).

The glycogen breaks down into glucose1-p after that glucose1-p convert into glucose6-p then its converted to glucose by enzyme call(phosphatase) then the glucose will go to blood stream

The mechanism of glycogen degradation to produce energy (in muscles)

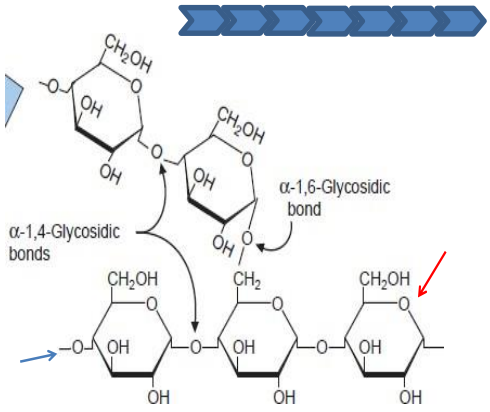
The glycogen breaks down into glucose1-p after that glucose1-p is converted into glucose6-p and gets stuck but why??, because in the muscles there is no phosphatase enzyme or glucose6-p transporter, so glycolysis begins

-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).

Now let's talk about degradation of glycogen(glycogenolysis) in details



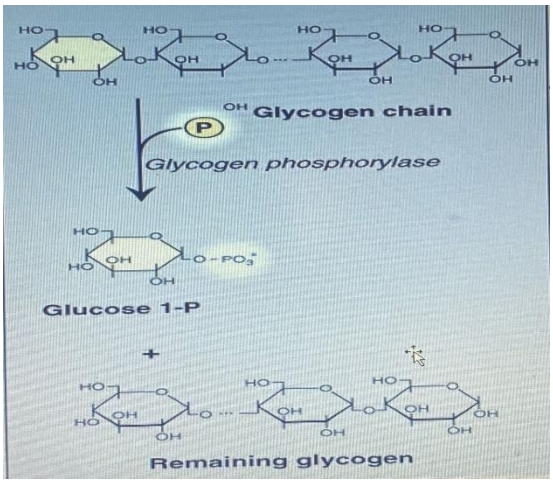
There are two enzymes involved in glycogenolysis One for breaking A (1,4) bonds and another one for A (1,6) bonds

-Degradation of glycogen One glucose unit is removed at a time

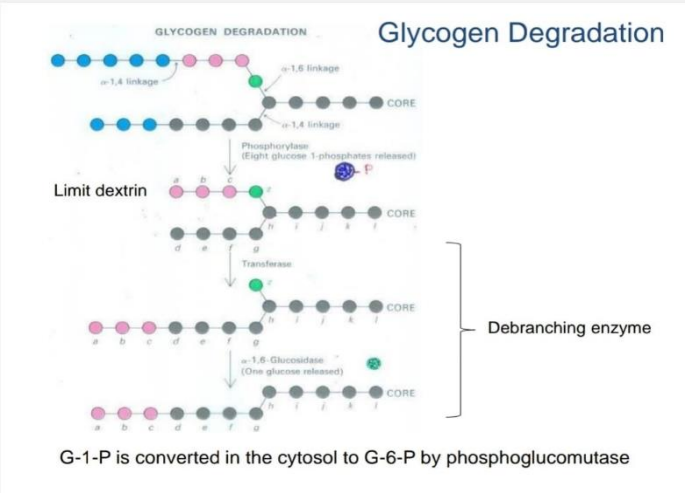
-Starts from the non-reducing ends

-Released in the form of glucose 1-phosphate

the enzyme that cuts A (1,4) bond call glycogen phosphorylase it breaks down glycogen to glucose then add phosphate to it so becomes glucose1-p
as we see in the picture



when the phosphorylase enzyme becomes close about 4 glucose residues to A (1,6) bond will stop and remain short chain of glucose this chain is called (limit dextrin) the remained 3 glucoses will transfer to another main chain by enzyme call (debranching enzyme)
this enzyme also breaks down A (1,6)



G-1-P is converted in the cytosol to G-6-P by phosphoglucomutase

in conclusion the debranching enzyme have two functions (transferase,
A (1,6) glycosidase)

The glucose release as glucose1-p then convert into glucose6-p by (phosphoglucomutase)

This is the main pathway to degradation of glycogen

The minor pathway for degradation is lysosomal degradation in cells

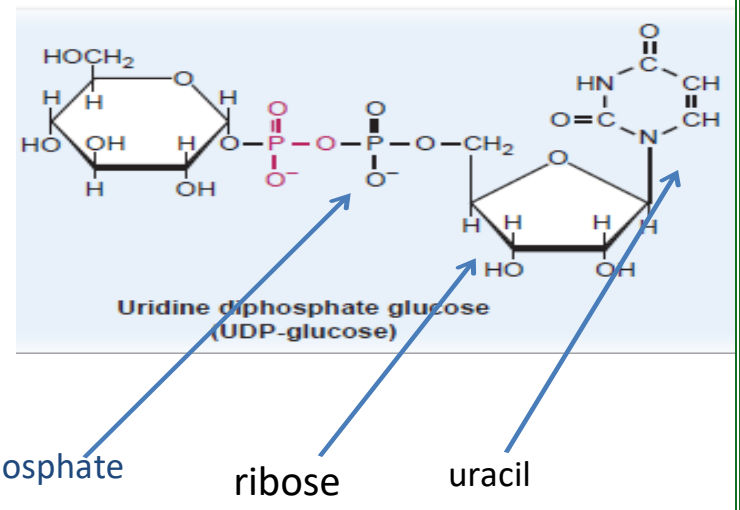
-A small amount (1–3%) of glycogen is degraded by the lysosomal enzyme, α (1–4)-glucosidase (acid maltase).

The purpose of this pathway is unknown.

A deficiency of this enzyme causes0

accumulation of glycogen in vacuolesin the lysosomes (Type II: Pompe disease)

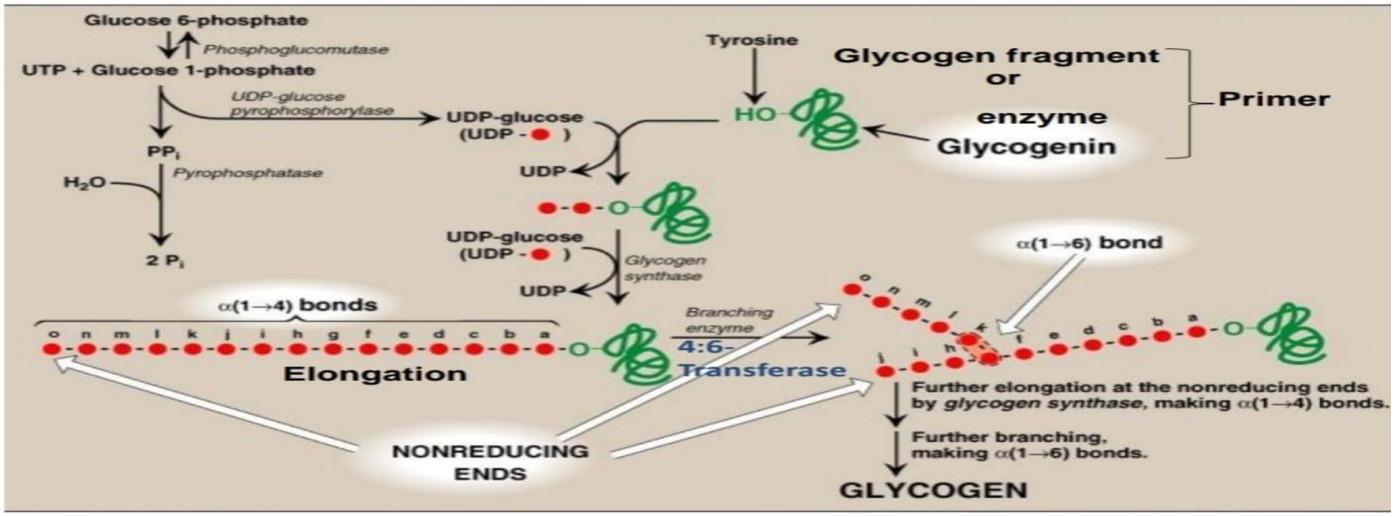
Note: UDP-glucose result from UTP and glucose1-p and release two phosphate from UTP not glucose1-p
Look at the red color in picture!



now let's talk about synthesis of glycogen(glycogenesis)

-Glycogen is synthesized by adding glucose one by one

-UDP-Glucose is the active donor of glucose units



As we know from previous page, the glucose6-p convert into glucose1-p by (phosphoglucomutase) and the then glucose1-p combines with UTP to produce UDP-glucose by (pyrophosphorylase) then it combines with residue of glycogen fragment or enzyme called (glycogenin) this enzyme contain terminal tyrosine to react with glucose by hydroxyl group after this UDP will be released by first carbon

Then another UDP-glucose binds by (glycogen synthesis) and UDP is released, and this process is repeated to consist long chain but not branched (elongation)

Now how do branches form? by enzyme called (branching enzyme or 4:6-transferase) this enzyme will cut down part of this long chain then add this part to the main chain and now we have two non-reducing ends and the process is repeated to form glycogen as we see in the picture

(Focus on the picture please

عشان هيك حطيناها قد راسك)

Now let's start a new topic

طيب هسا هاض الموضوع بسيط كثير وهو للامانة نتيجة فهمنا لباقي المحاضرة لانه بعتمد عالانزيمات اللي حكينا عنها قبل شوي اللي ظللناهم بالاصفر ركزوا عليهم كثير وشو بسووا اوك!!!!!

وبعينا الله بدنا نحفظ شوي

-Glycogen Storage Diseases

-Genetic diseases

-Defect in an enzyme required for synthesis or degradation leads to

-Accumulation of excessive amount of abnormal glycogen (synthesis) or ---normal glycogen (degradation)

-In one or more tissue

-Severity: FATAL in Infancy……. Mild disorder

If we have problem in enzymes involved in synthesis of glycogen it leads to synthesis abnormal glycogen but when we have problem in enzymes that involved in degradation it leads to accumulation of glycogen

1-Glycogen Storage Diseases

I Glucose-6-phosphatase (von Gierke disease)

Liver, kidney, and intestine.

Severe fasting hypoglycemia(نقص السكر بالدم)

Hepatomegaly fatty liver.

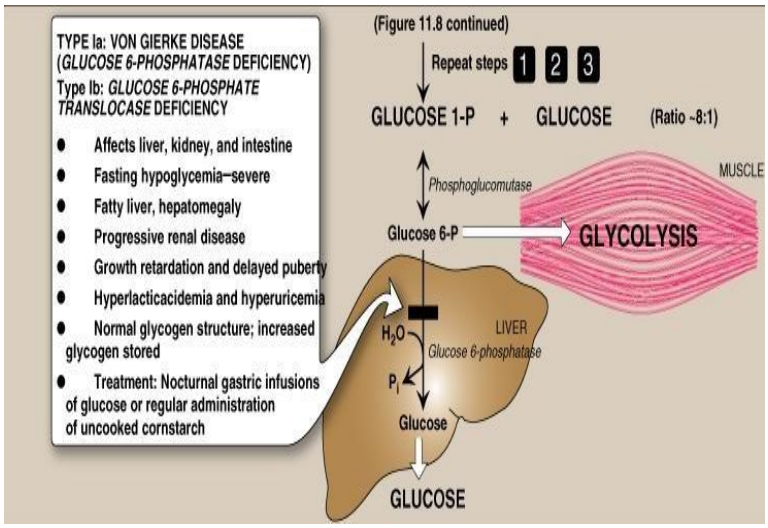
(تضخم بالكبد وبتكون عليه دهون)

Normal glycogen structure.

(Because it is related to degradation enzyme)

Progressive renal disease.

Growth retardation.



2-Glycogen Storage Diseases

V Muscle glycogen phosphorylase (McArdle syndrome)

-Skeletal muscle glycogen phosphorylase deficiency

-Only muscle is affected;

-Weakness and cramping of muscle after exercise

-no increase in [lactate] during exercise

(Because the lactate comes from pyruvate and pyruvate will not form)

3-Glycogen Storage Diseases

-II Lysosomes α (1→4) glucosidase ---POMPE Disease

-Degradation of glycogen in the lysosomes

≈ 3% of glycogen is degraded in the lysosomes

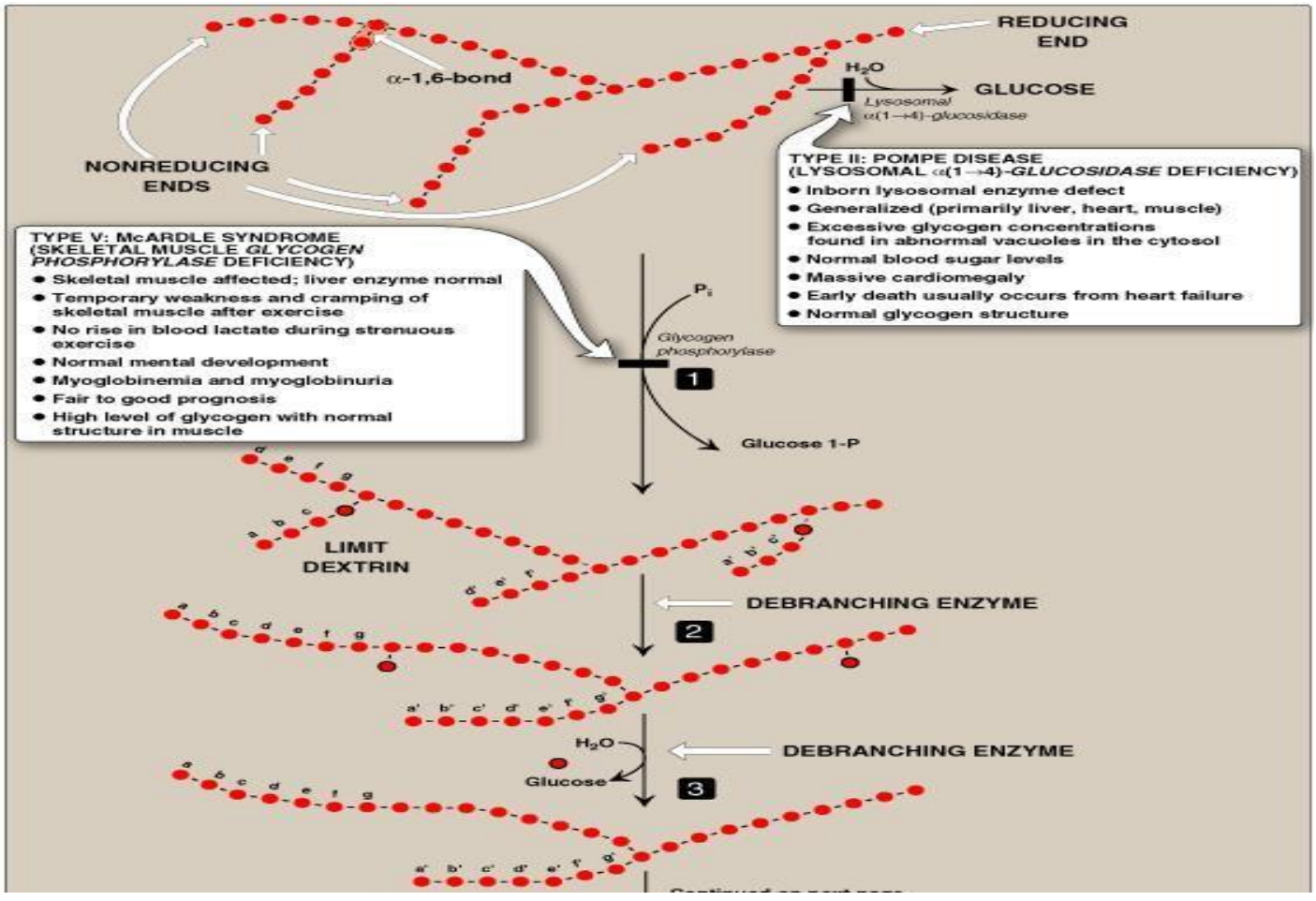
-Affects liver, heart, and muscle

-Excessive glycogen in abnormal vacuoles in the lysosomes

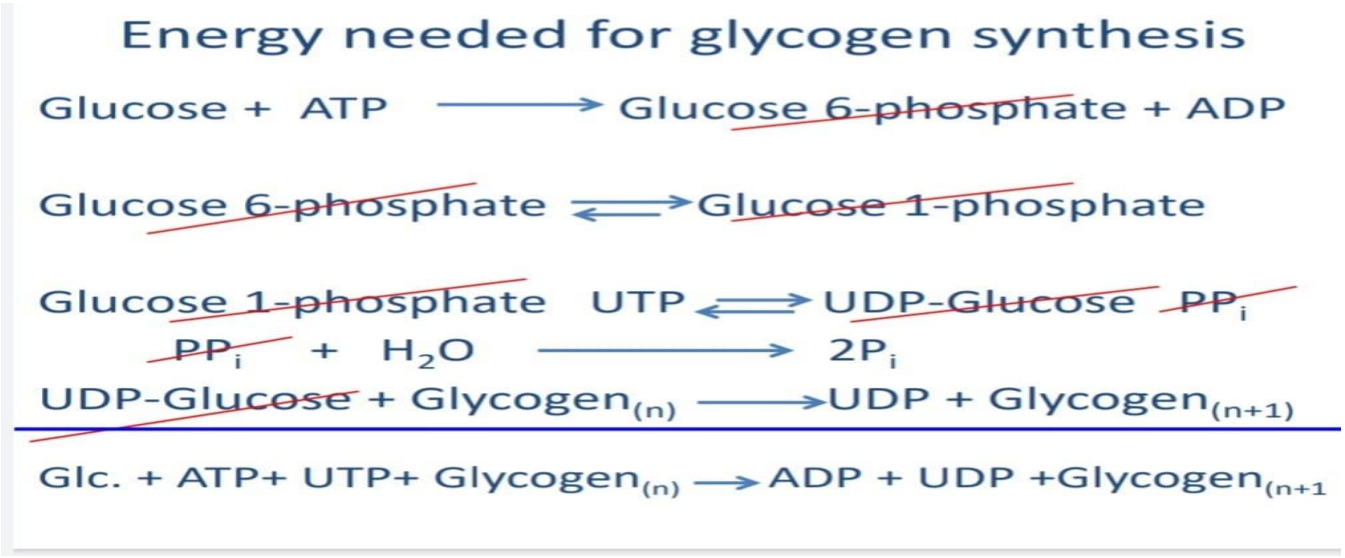
Massive cardiomegaly (تضخم عضلة القلب)

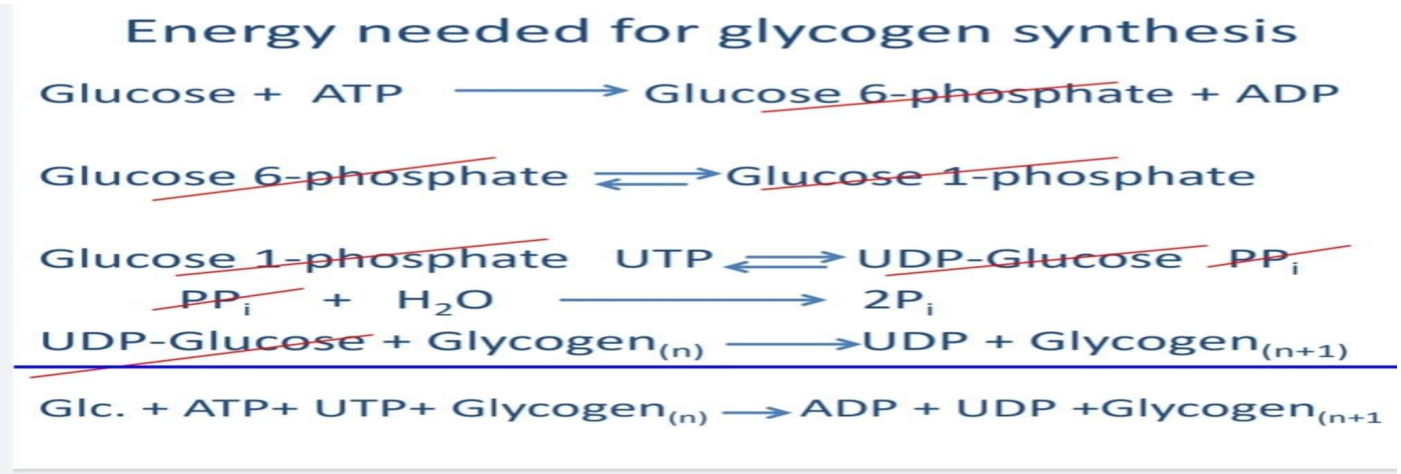
- **Normal blood sugar, normal glycogen structure**

Early death from heart failure.



- **The net reaction in glycogen synthesis and degradation**





In conclusion in synthesis, we need to one ATP and one UTP to add one glucose into glycogen chain, and to degrade glycogen we need to non-organic phosphate

Past paper

1) The enzyme which is involved in glycogen metabolism and does not exist in muscles are:

A) Glycogen synthase

B) Glucose 6 phosphatase

C) Glucose 1 phosphatase

D) Glycogen phosphorylase

2) POMPE disease is caused by a deficiency in:

A) Glucose 6 phosphatase

B) Glycogen phosphorylase

C) Lysosomal glucosidase

D) Phosphoglucomutase

3)The active form of glucose required by glycogen synthase is

a. UDP-Glucose.

b. Glucose 6-Phosphate.

c. Glucose l-Phosphate.

d. UTP-Glucose.

e. ADP-Glucose

4)The immediate product(s) of glycogen degradation by glycogen phosphorylase in the liver is(are)

a. glucose 1,6– bisphosphate.

b. glucose 1-phosphate.

c. glucose 6-phosphate.

d. glucose.

e. all answers are true.

5-someone suffering from hypoglycemia between meals, he has high levels of free fat in blood (something like that), high glycogen levels but normal structure & enlarged liver. What is the problem?

a) Phosphoglucomutase deficiency

b) Glycogen phosphorylase deficiency

c)Glucose-6-phosphatase deficiency

6-The active form of glycogen _____ is phosphorylated; the active form of glycogen _____ is dephosphorylated.

a. hydrolase; dehydrogenase

b. dehydrogenase; hydrolase

c. hydrolase; synthase

d. phosphorylase; synthase

e. synthase; phosphorylase

7-In glycogen, the chains are formed by _____ glycosidic linkages while the branches are _____ glycosidic linkages.

a. alpha-1,4; alpha-1,6

b. alpha-1,6; alpha-1,4

c. beta-1,4; alpha-1,6

d. beta-1,6; alpha-1,4

e. none of the above

8-The formation of primers to initiate glycogen synthesis is carried out by:

a. glycogenin

b. oxidase

c. reductase

d. kinase e. synthase

answers

1-b, 2-c, 3-a ,4-b ,5-c ,6-d ,7-a ,8-a

-Excess glycogen in muscle with normal blood sugar and is a problem in muscle's:

Answer: glycogen phosphorylase

- Involved in both glycogen lysis and glycogen synthesis:

Answer: Production of glucose 1 p

-Common between glycogen synthesis and degradation:

Answer: Phosphoglucomutase

تجري الرياح كما شاء الإله لها

لله نحن وموج البحر والسفن