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Glycogen Metabolism

Color Index:

- Original content
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- Only in girls' slides
- Only in boys' slides

Biochemistry team 438

Objectives:

Slide No. 3
1. The need to store carbohydrates in muscle
2. The reason for carbohydrates to be stored as glycogen

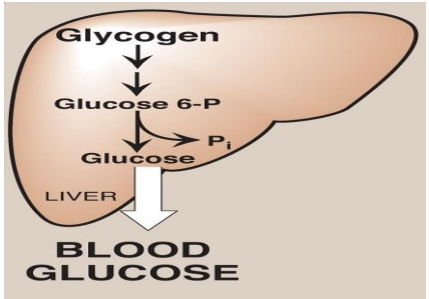
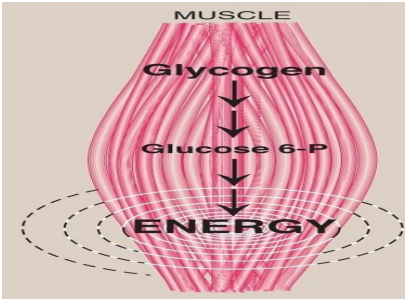
Slides (6,7)
3. An overview of glycogen synthesis (Glycogenesis)

Slides(9,10)
4. An overview of glycogen breakdown (Glycogenolysis)

Slide No.12
5. Key elements in regulation of both Glycogenesis and Glycogenolysis

Objectives: 1,2

Location and function of glycogen

location	Liver	Skeletal muscle
Weight of glycogen	100 g	400 g
Percentage of the total organ wight	10% of a well-fed (healthy) adult liver	1-2% of the weight of resting muscle
Function	**Major:** source for blood glucose (especially during early stages of fasting 10-17 hours) "during late stages gluconeogenesis occurs" **Minor:** fuel reserve for hepatic cells	fuel reserve (ATP) (during muscular exercise)
Pathway	Glycogen → Glucose 6-P → Glucose 	Glycogen → Glucose 6-P → Energy 

★ Extra info:

why muscles never make glucose?

1. the aim of glycogenolysis in muscle cells is to generate energy, so it's better to start from glucose 6-P rather than glucose to avoid losing 1 ATP.

2. The hormone Glucose 6-phosphatase which responsible for the formation of glucose from glucose 6-P is only present in the live

Structure of Glycogen

branched-chain homopolysaccharide

★ made exclusively from α - D-glucose

α (1→4) Glycosidic linkage

★ Between glucose residues

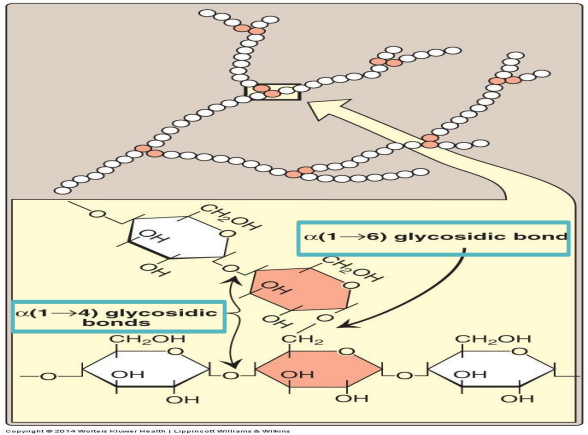
➔ (linear)

➔ The primary glycosidic bond

α (1→6) Glycosidic linkage

★ in branches

➔ every 8 to 10 residues



in the form of granules

★ present in the **cytoplasm**

(it can be found in all cells but mainly in liver & muscle)

➔ these granules also contain

enzymes necessary for glycogen **synthesis**

enzymes necessary for glycogen **degradation**

★ These are different enzymes

Metabolism of Glycogen in Skeletal Muscle

1- Glycogenesis:(Anabolism)
Synthesis of Glycogen from glucose

2- Glycogenolysis : (catabolism)
Breakdown of Glycogen to Glucose-6-phosphate
"not to glucose"

Glycogenesis

Synthesis of Glycogen in skeletal muscles

1) Building blocks
UDP-GLUCOSE (UDP: uridine diphosphate)
★ Source of glucose molecules(energy) , UDP carries the glucose but it is not added to the elongated chain.
(get removed in the elongation step)

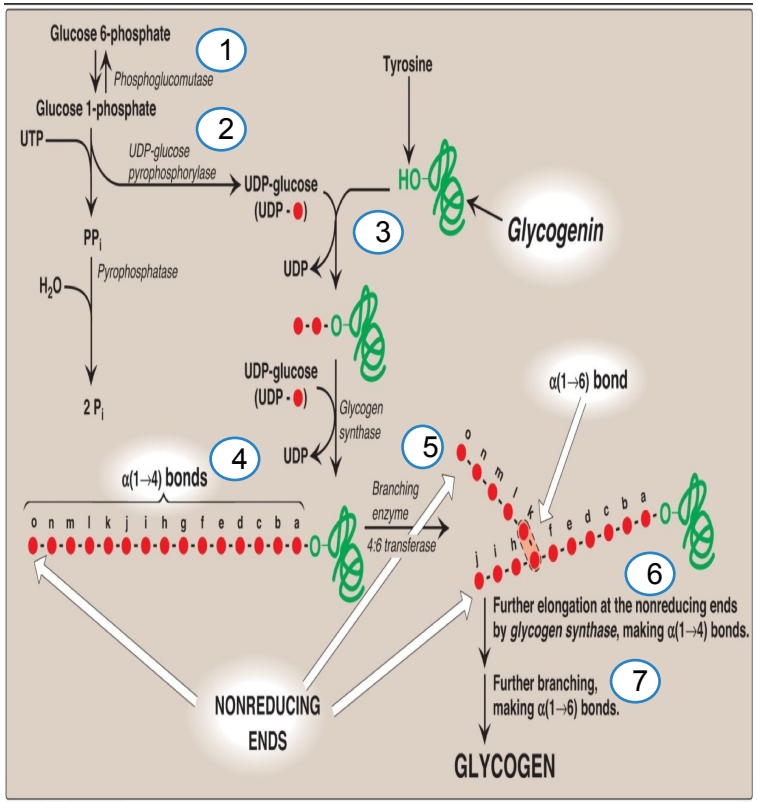
2) Initiation of synthesis (either by):
A. Elongation of pre-existing glycogen fragment
B. The use of glycogen primer. (Glycogenin)

*option B is like DNA replication we can't start from scratch so we need an enzyme to make a primer (glycogenin in glycogenesis or primase in DNA replication)
EXCEPT in glycogenesis The primer doesn't get removed

3) Elongation
Using the enzyme **glycogen synthase for (α 1-4 linkages)**
★ Glycogen synthase cannot initiate synthesis but only elongates pre-existing glycogen fragment or glycogen primer + removes the UDP

4) Branching:
Using **branching enzymes for (α 1-6 linkages)**

Synthesis of Glycogen



1- Glucose 6-P + phosphoglucomutase (Isomerization) → Glucose 1-P

-UDP: is an important factor in glycogenesis.

-Before glucose can be stored as glycogen in the liver and muscles, the enzyme UDP-glucose pyrophosphorylase forms a UDP glucose complex

2- Glucose 1-P + UTP (energy) + UDP-glucose pyrophosphorylase (enzyme) → UDP-glucose unit.

- Meanwhile the glycogenin is making the primer.

3- Start of elongation by **removing** of UDP and **adding** of glucose to the primer by glycogen synthase (enzyme)

-Branching speeds up the process of synthesis of glycogen, so:
After having at least 8-10 residues:

-and by the (Branching enzyme 4:6 transferase) *the name in a simple term which is the one you should know :

4- **breaking** the (α 1→4 linkage) of 4-6 residues minimum.
5- transfer the 4-6 residues to a different site and **making** a (α 1→6 linkage).

* Nonreducing end is when the anomeric carbon is attached to something else.

the most important enzyme of Synthesis of Glycogen

Enzyme	function
phosphogluco-mutase	**Isomeration from G6P to G1P**
UDP-glucose pyrophosphorylase	forms a UDP glucose complex
glycogenin	making the primer
glycogen synthase	Start of elongation
4:6 transferase	Branching enzyme

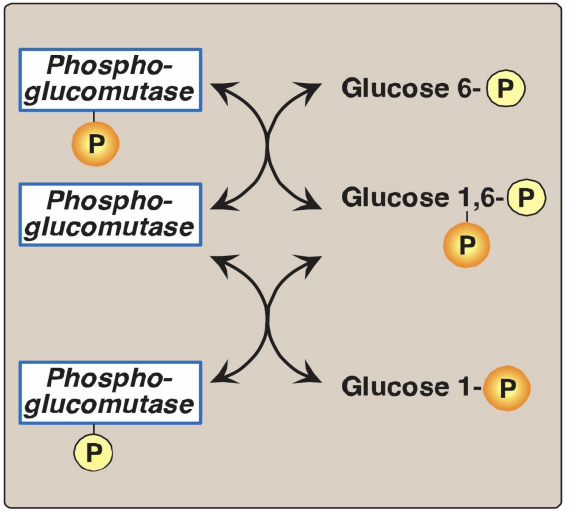


Figure 11.6
Interconversion of glucose 6-phosphate and glucose 1-phosphate by *phosphoglucomutase*. P = phosphate.

Glycogenolysis

Breakdown of Glycogen to Glucose-6-phosphate in skeletal muscle.

1-Shortening of glycogen chain: by glycogen phosphorylase

Glycogen phosphorylase contains a coenzyme: pyridoxal phosphate (PLP)

They cleave (break) α(1→4) bonds of the glycogen chain → Producing Glucose 1-phosphate Note: After it reaches 4 residues the enzyme will stop cleaving

G1P is converted to glucose 6-phosphate by mutase enzyme - (phosphoglucomutase)

2-Removal of branches: by debranching enzymes

Cleaving of α(1→6) bonds at the branches of glycogen which releases free glucose

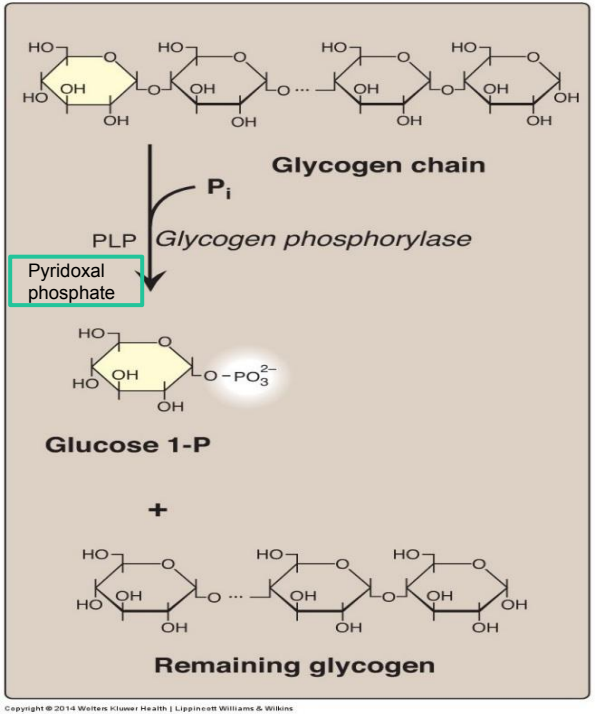
*in few quantities because the majority of the bonds are α (1→4) bonds

3-Fate of glucose 6-phosphate (G-6-P)

G-6-P is not converted to free glucose

.(it is converted to free glucose only in the liver)

It is used as a source of energy for skeletal muscles during muscular exercise (by anaerobic glycolysis starting from G-6-P step



*Pyridoxal phosphate (coenzyme) = vitamine B12

.. continue

1) LIMIT DEXTRIN:

in this point the glycogen phosphorylase can`t continue shorting the chine (it remains)

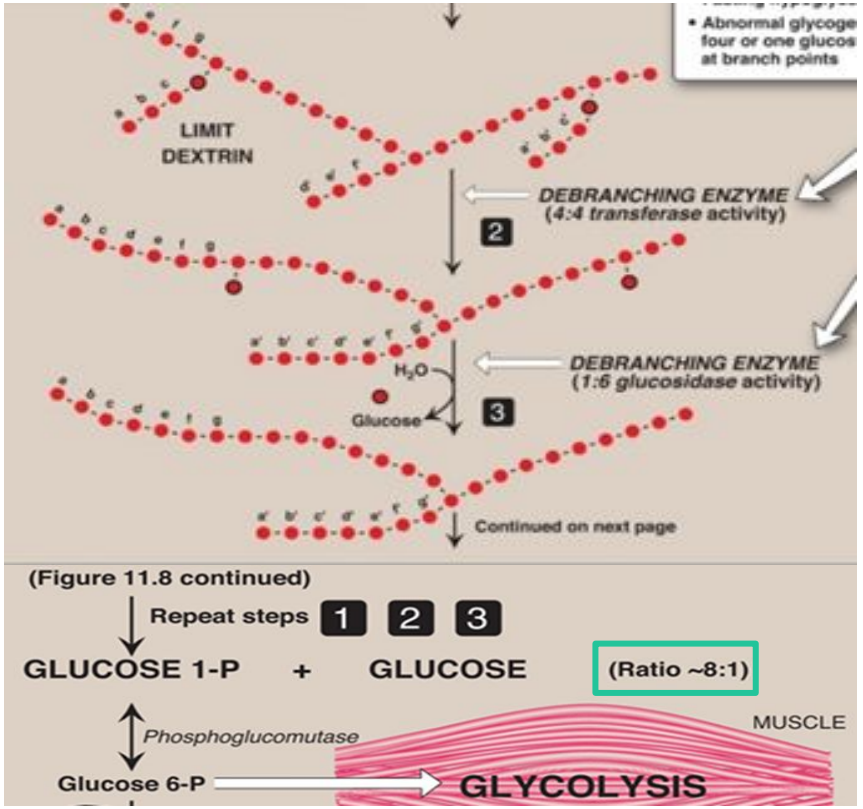
2) debranching enzyme 4:4 transferase:

take three glucose molecules by breaking α(1→4) bonds from one end and bind it to the other end

3) debranching enzyme 1:6 glucosidase:

it's **the same enzyme** above except that unbind the α(1→6) bonds

*every 8 molecules of G-1-P, one molecule of free glucose will be produced)



the most important enzyme of Glycogenolysis

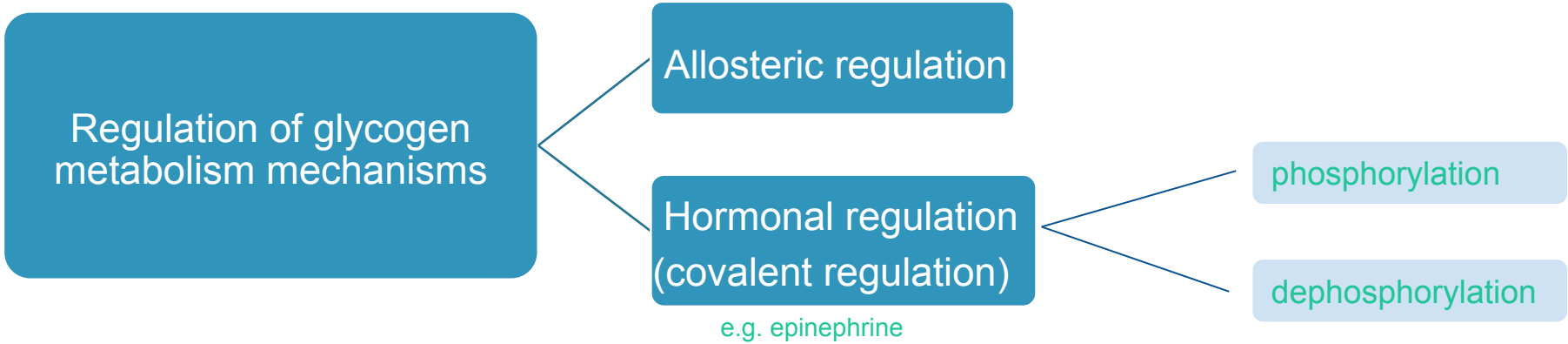
Enzyme	function
glycogen phosphorylase	Chain shortening
pyridoxal phosphate	coenzyme of glycogen phosphorylase
mutase enzyme (phosphogluco-mutase)	convertes G1P to G6P
debranching enzymes 4:4 transferase	take three glucose & bind it to another branch
debranching enzymes 1:6 glucosidase	unbind the 1:6 linkage

Regulation of Glycogen Metabolism.

Synthesis & degradation of glycogen are tightly regulated

In Skeletal Muscles:

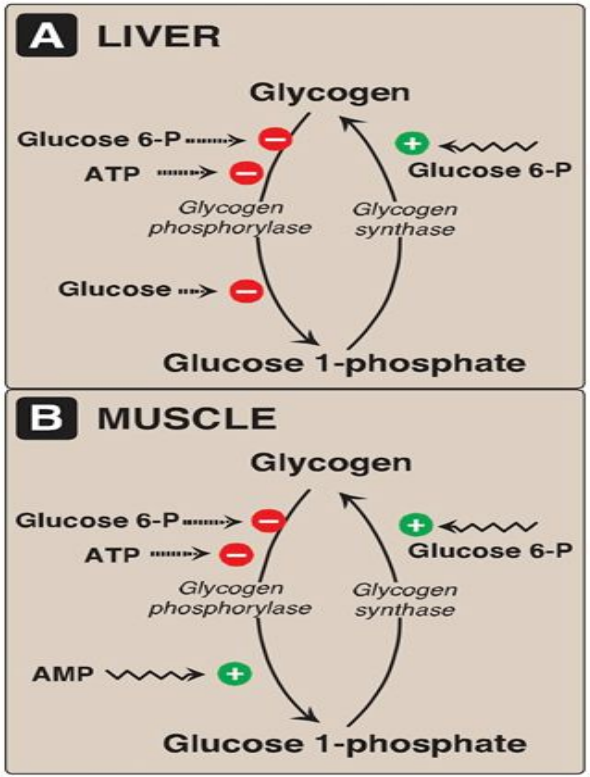
- Glycogen **degradation** occurs during **active exercise**
- Glycogen **synthesis** begins when the **muscle is at rest**



★ These enzymes are important

1- Allosteric Regulation

in skeletal muscles (in liver is extra)



Glycogen phosphorylase

- **-Inhibited by:**(Inhibit glycogen break down)
- -glucose 6-p (High energy signal in the cell end product of the pathway).
- - ATP (ATP is abundant, no need for more energy).

- **-Activated by:**(activate glycogen break down)
- - Ca++ (we will explain it in the next slide).
- - AMP (low energy signal).

Glycogen synthase

- Activated by: (activate glycogen synthesis)

- Glucose 6-p (High energy signal in the cell)

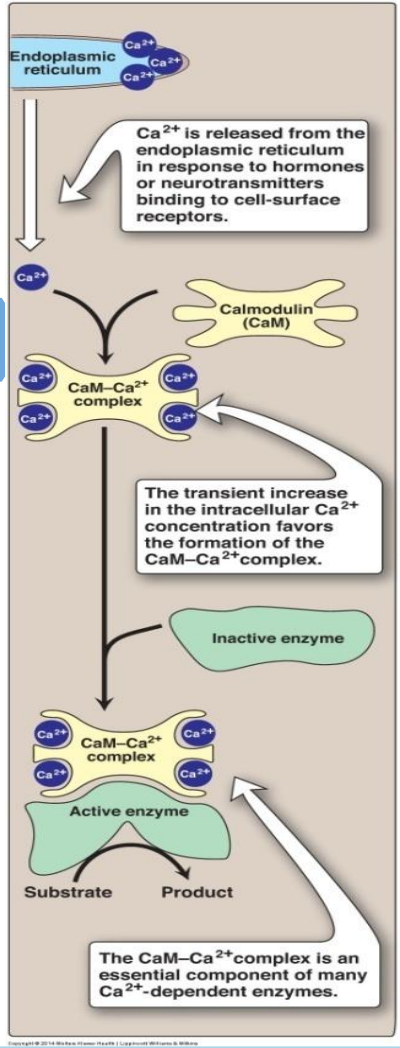
mechanism of Allosteric Regulation

exercising	muscle contraction	Increase of calcium	Formation of Ca+2 -calmodulin complex	Activation of Ca2+ dependent enzyme	Glycogen degradation

"recall the mechanism of muscle contraction from physiology : the calcium comes out from sarcoplasmic reticulum during muscle contraction".

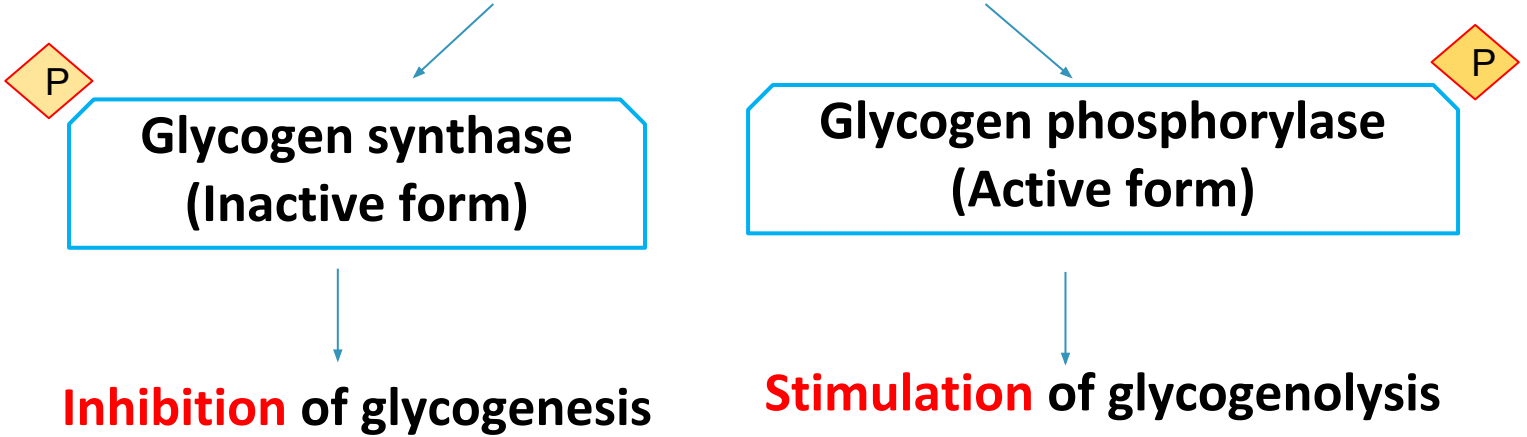
"because of high concentration of Ca+2 intracellularly".

- e.g. glycogen phosphorylase.



2- Hormonal Regulation

1. Muscle contraction
2. Epinephrine release
3. Skeletal muscle: Epinephrine/receptor binding
4. Second messenger: cAMP (Activate protein kinase A)
5. Response: Enzyme phosphorylation



Glycogen storage Diseases (GSD)

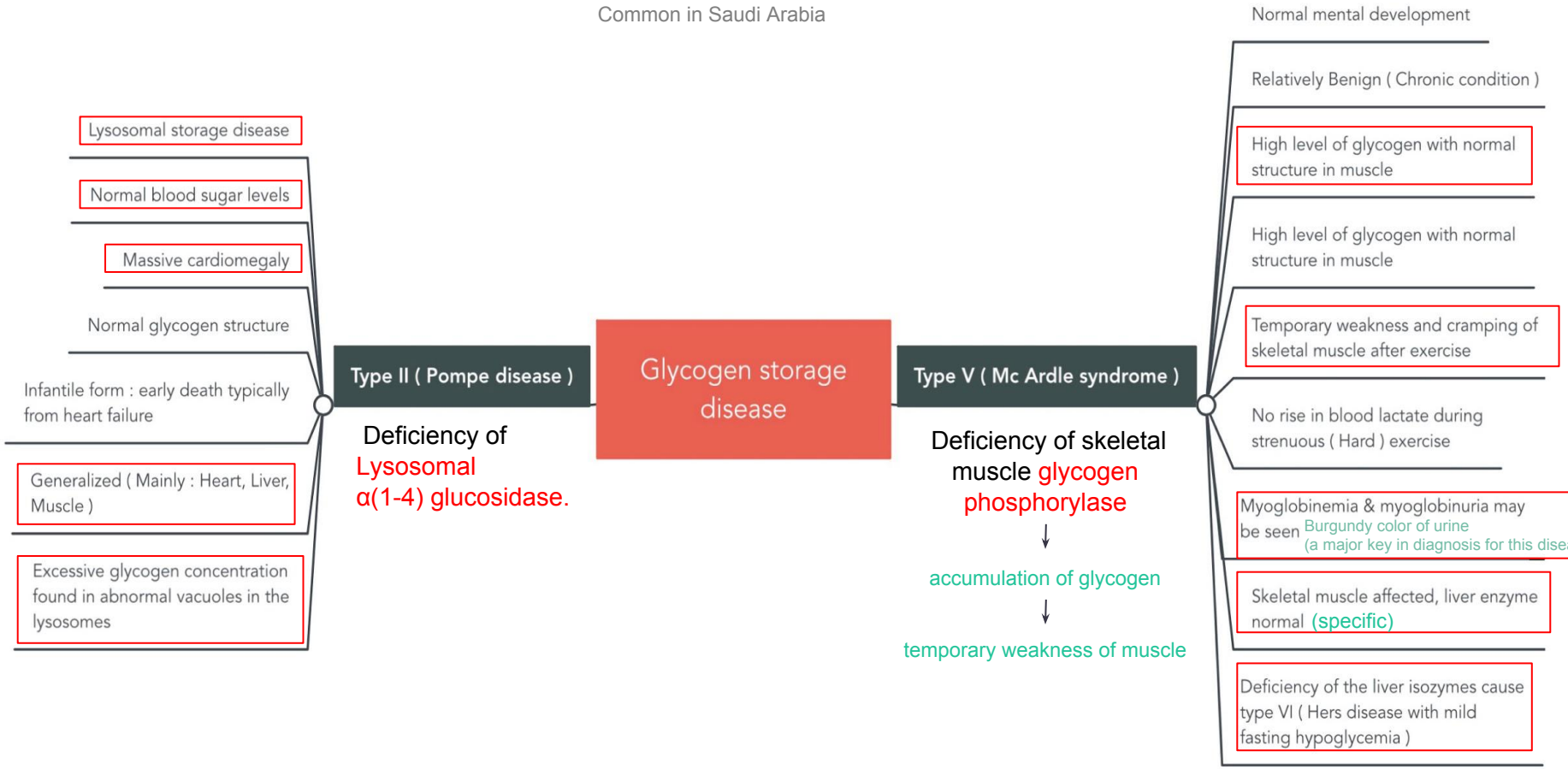
- A group of genetic diseases that result from a defect in

an enzyme required for :

a) *glycogen synthesis* → Result in : → Formation of **abnormal** glycogen structure

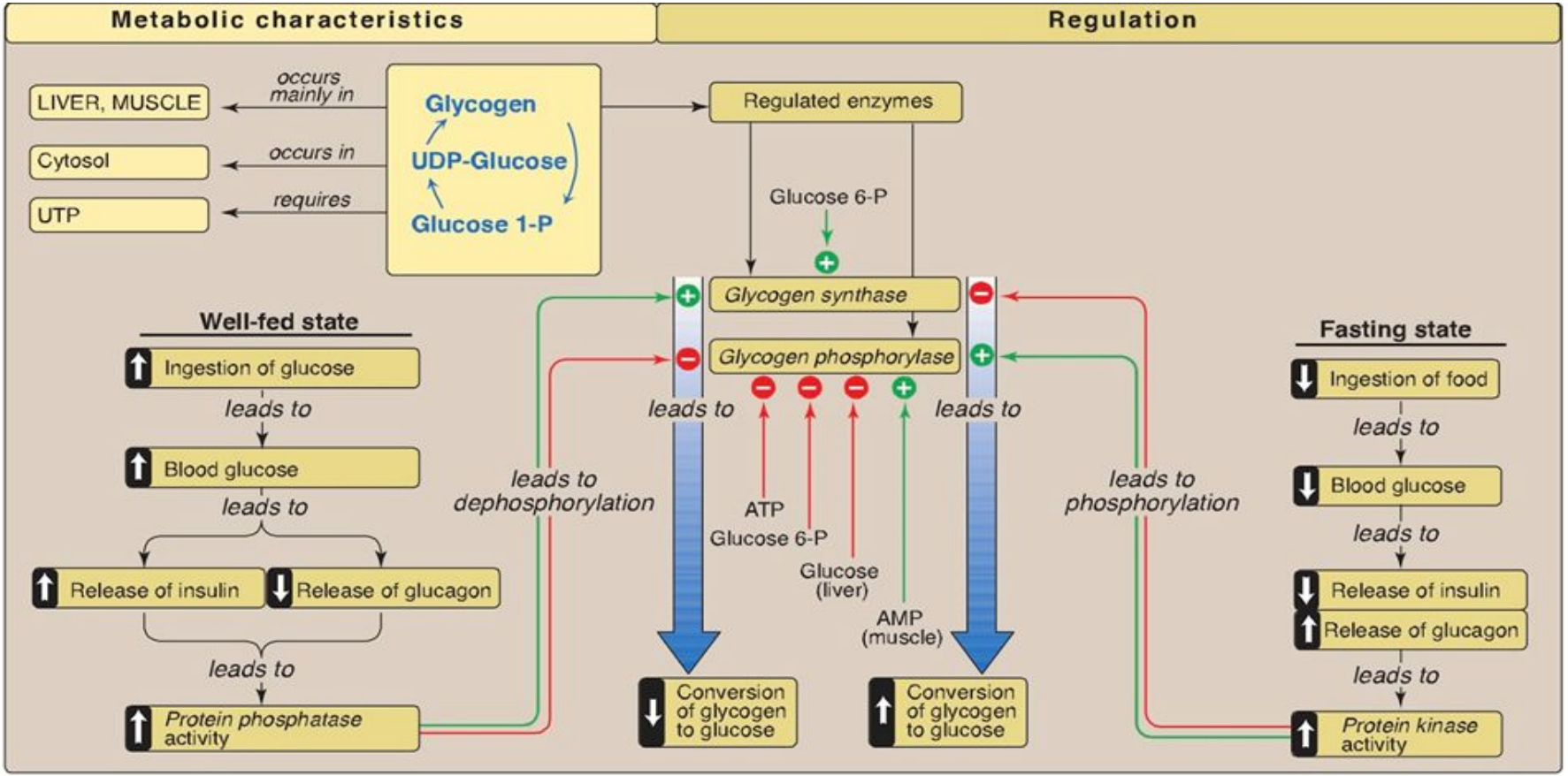
b) glycogen degradation → Excessive accumulation of **normal** glycogen in a specific tissue.

Glycogen storage Diseases (GSD)



the brief about the diseases are useful in question as cases

Review


Metabolic characteristics
Regulation
LIVER, MUSCLE
occurs mainly in
Cytosol
occurs in
UTP
requires
Glycogen
UDP-Glucose
Glucose 1-P
Regulated enzymes
Glucose 6-P
Glycogen synthase
Glycogen phosphorylase
Well-fed state
Ingestion of glucose
leads to
Blood glucose
leads to
Release of insulin
Release of glucagon
leads to
Protein phosphatase activity
leads to dephosphorylation
leads to
leads to
ATP
Glucose 6-P
Glucose (liver)
AMP (muscle)
Conversion of glycogen to glucose
Conversion of glycogen to glucose
leads to phosphorylation
Fasting state
Ingestion of food
leads to
Blood glucose
leads to
Release of insulin
Release of glucagon
leads to
Protein kinase activity

MCQs

Q1: The first product formed during glycogenolysis (glycogen degradation at alpha 1,4 glycosidic bonds) is:			
A) Glucose	B) glucose 1 phosphate	C) glucose 6 Phosphate	D) glucose 1,6 bisphosphate
Q2:A 23 years old male came to the clinic complaining from muscle cramps and pain, after examination you found high levels of glycogen with normal structure in muscle, and no rise in blood lactate during strenuous exercise. The patient most likely have :			
A)GSD Type V	B)GSD Type II	C)GSD Type III	D) GSD Type 1
Q3:The glycogen become glucose 1-phosphate, the enzyme used for this reaction is :			
A)Glycogen synthase	B)Glycogen phosphorylase	C)Phosphoglucomutase	D) glycogenin
Q4:debranching enzyme			
A)1:6 glucosidase	B)4:4 transferase	C)4:6 transferase	D)A&B
Q5:what is percentage of of the weight of 100 g of glycogen in a healthy adult liver			
A) 10%	B)100%	C)20%	D)50%
Q6:Glycogen phosphorylase can be activated by			
A)UDP	B)ATP	C)ADP	D)AMP

Answer key:

1) B
2) A
3) B
4) D
5) A
6) D

SAQs

Q1:Glycogen phosphorylase enzyme activity inhibited by?

Glucose 6-phosphate, ATP

Q2:What happen to the glycogen if the muscle was at rest?

Glycogen synthesis begin

Q3 name the steps of Synthesis of Glycogen from glucose

building blocks , initiation , elongation , branching

Q4:Name two enzyme that help in glycogenolysis and their function

1-4:4 transferase: debranching enzyme

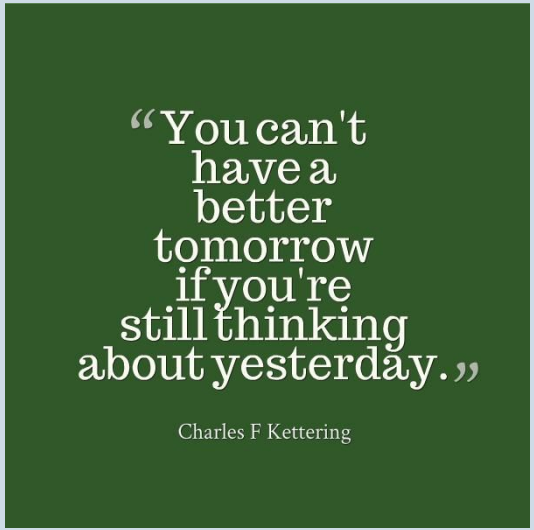
2- mutase enzyme: convertes G1P to G6P

❖ Team leaders:

ديما المزيد — رائد العجيري

- ❖ Girls team:
  - ريم القرني
  - طيف العتيبي
  - نوره المزروع
- ❖ Boys team:
  - مهند القرني
  - سعد دماس
  - عمر الغامدي

Wish you all the best !



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