بسم الله الرحمـٰن الرحيم

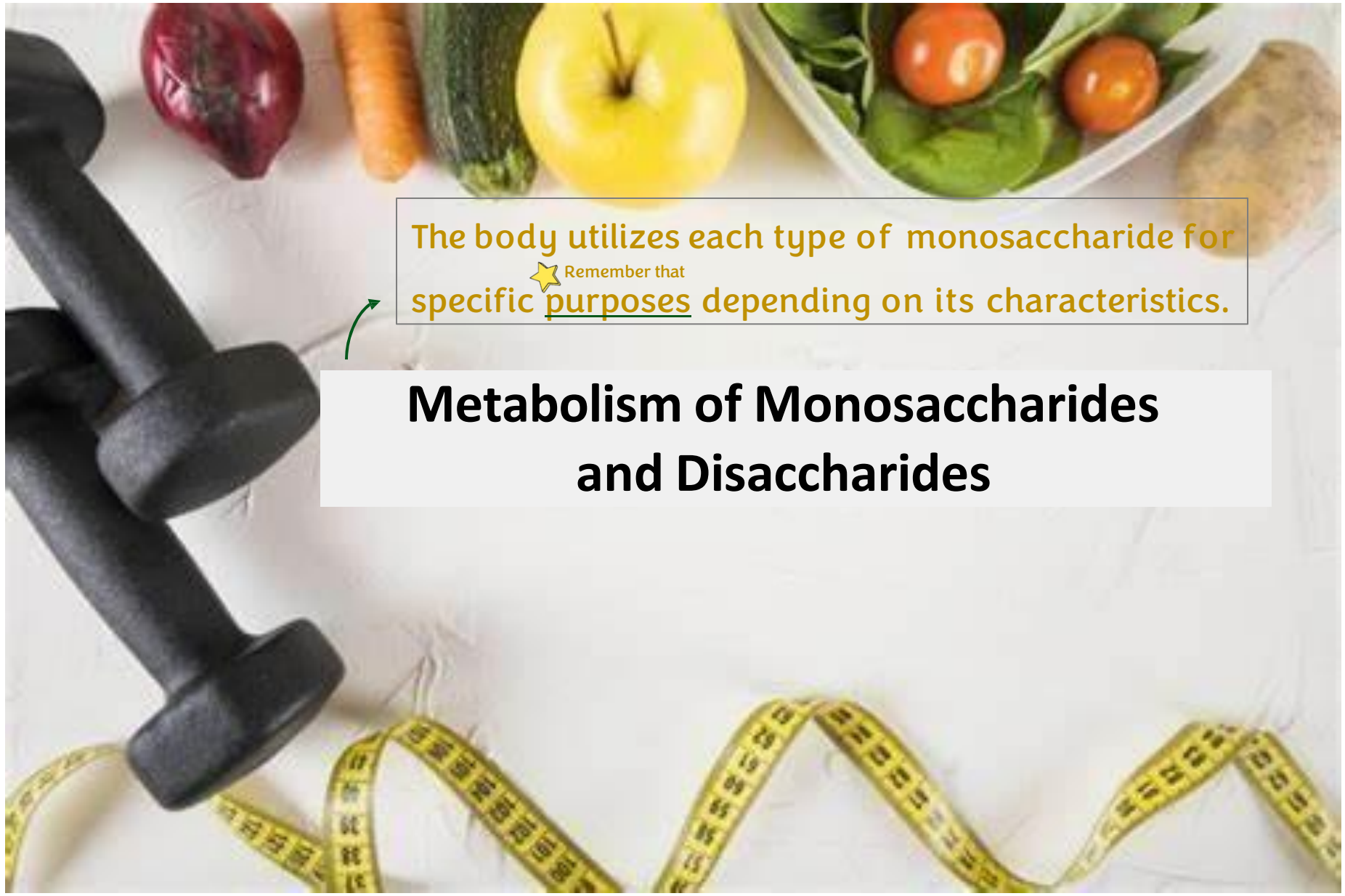
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Metabolism | FINAL 2

Metabolism of Monosaccharides & Disaccharides pt.1

Written by : DST

Reviewed by : NST



Metabolism of Monosaccharides and Disaccharides

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Fructose Metabolism

- 10% of the daily calorie intake.

  However, this is not a constant percentage and can vary depending on your diet type.

- Sources: sucrose, Fruits, honey, high-fructose corn syrup.

  High-fructose corn syrup, which contains a mixture of fructose and glucose, is commonly used as a sweetener in many processed foods. However, its health effects have been widely debated.

- Entry into cells is not insulin dependent.

  Unlike glucose, which can enter cells through insulin-dependent transporters like GLUT4, fructose uptake is insulin-independent by GLUT5 mainly.

- Does NOT promote the secretion of insulin.

The primary purpose of fructose metabolism is to generate energy.

Glucose increases blood sugar levels and insulin secretion, while **fructose** is metabolized in the liver without significantly impacting blood sugar directly, but excessive fructose intake can have long-term negative effects on metabolism and insulin sensitivity, so the effect of fructose on blood sugar level is debated upon.

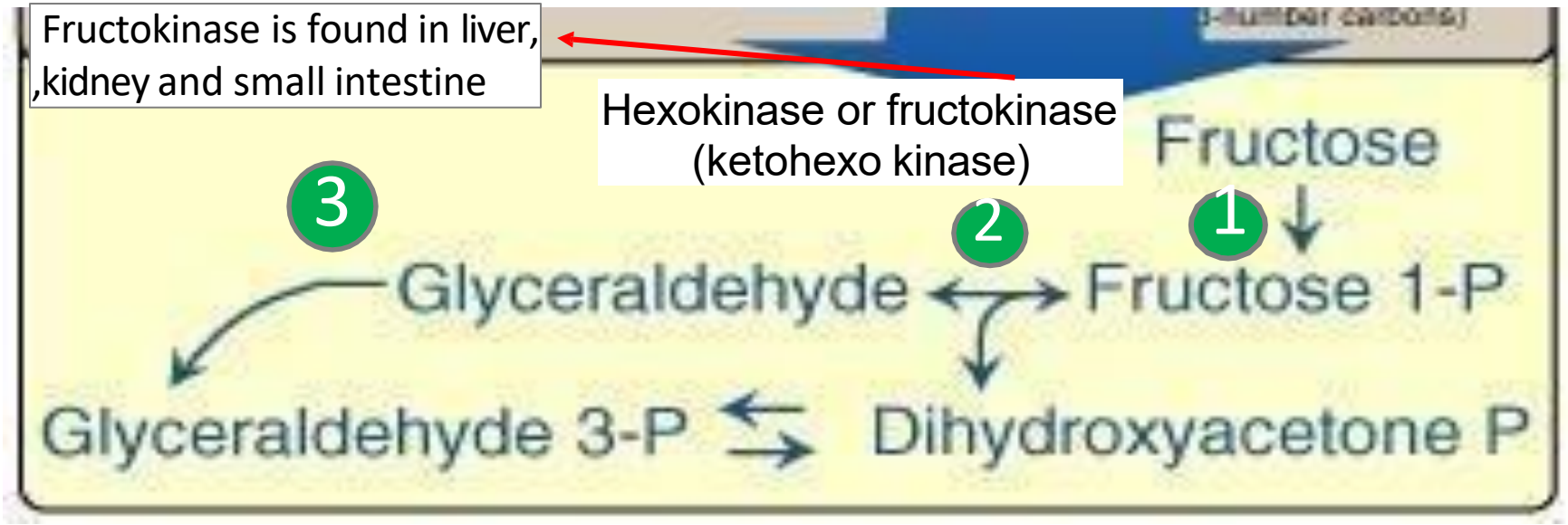
Fructose metabolism occurs through two main pathways:

1. Fructose-specific pathway (Fructose metabolism in the liver):

1. **Fructose phosphorylation**: Fructose is first phosphorylated by fructokinase (also called ketohexokinase) to form fructose-1-phosphate.
2. **Cleavage**: Fructose-1-phosphate is then split by aldolase B into two three-carbon molecules: Dihydroxyacetone phosphate (DHAP) & Glyceraldehyde.
3. **Conversion to glycolytic intermediates**:

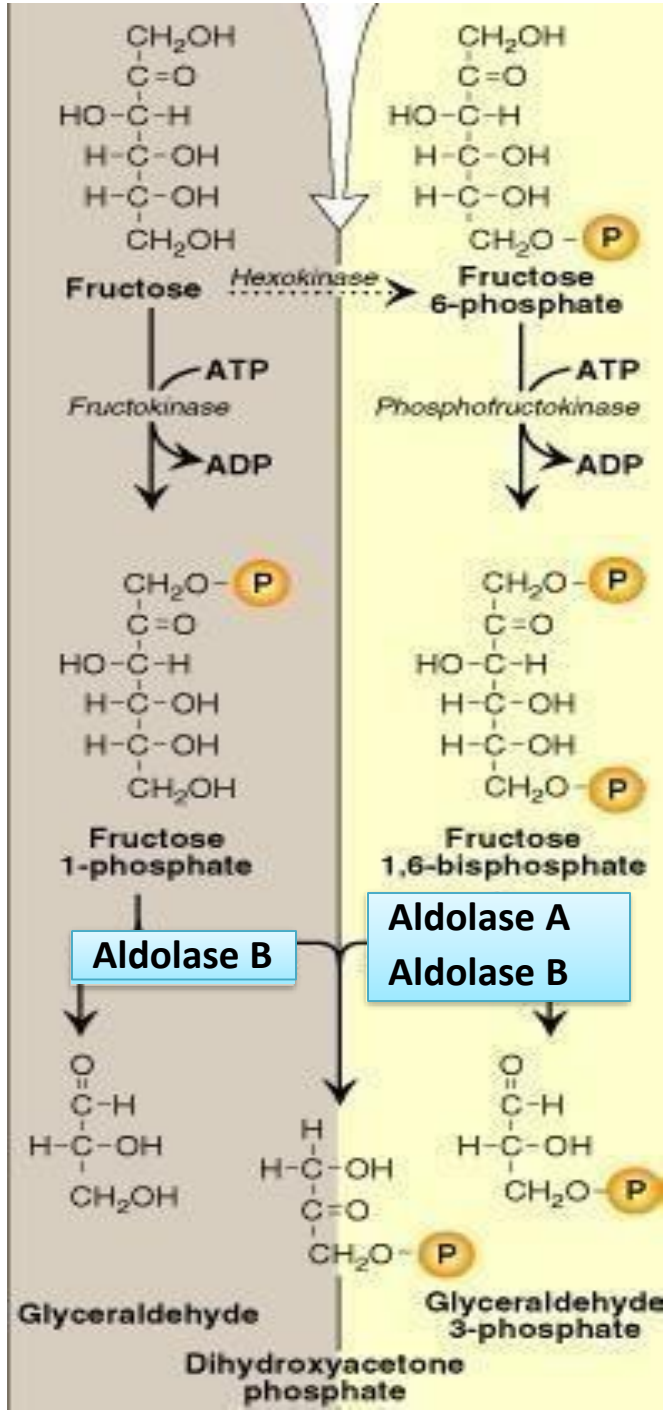
- **Glyceraldehyde** must be phosphorylated to glyceraldehyde-3-phosphate (G3P) to join glycolysis (by glyceraldehyde kinase.)
- Both **DHAP** and **G3P** can then enter the **glycolytic pathway.**

2. Non-specific, general pathway. See the next slide for explanation.



2. Non-specific, general pathway:

- **Hexokinase** phosphorylates fructose directly to form **fructose-6-phosphate (F6P)**, bypassing the second step of glycolysis (the isomerization).
- **Phosphofructokinase 1** then phosphorylates **F6P** to form **fructose-1,6-bisphosphate**.
- **Aldolase** (either A or B isoform) cleaves it into **glyceraldehyde-3-phosphate (G3P)** and **dihydroxyacetone phosphate (DHAP)**.



Fructose Metabolism

1. The specific pathway.

The specific pathway is more favorable because it bypasses the PFK-1step, which is a rate-limiting step (very slow) in glycolysis, allowing for faster and more efficient fructose metabolism.

2. The non-specific pathway.

Hexokinase affinity to fructose is low

- The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass *phosphor fructokinase-1-P* the major rate-limiting step in glycolysis.

Human expresses three forms of aldolase

Aldolase B

- Works in both the specific and non-specific pathways.
- Liver, kidney, small intestine.
- Substrate Fruc. 1 phopsphate Also Fruc. 1,6 bisphospate.

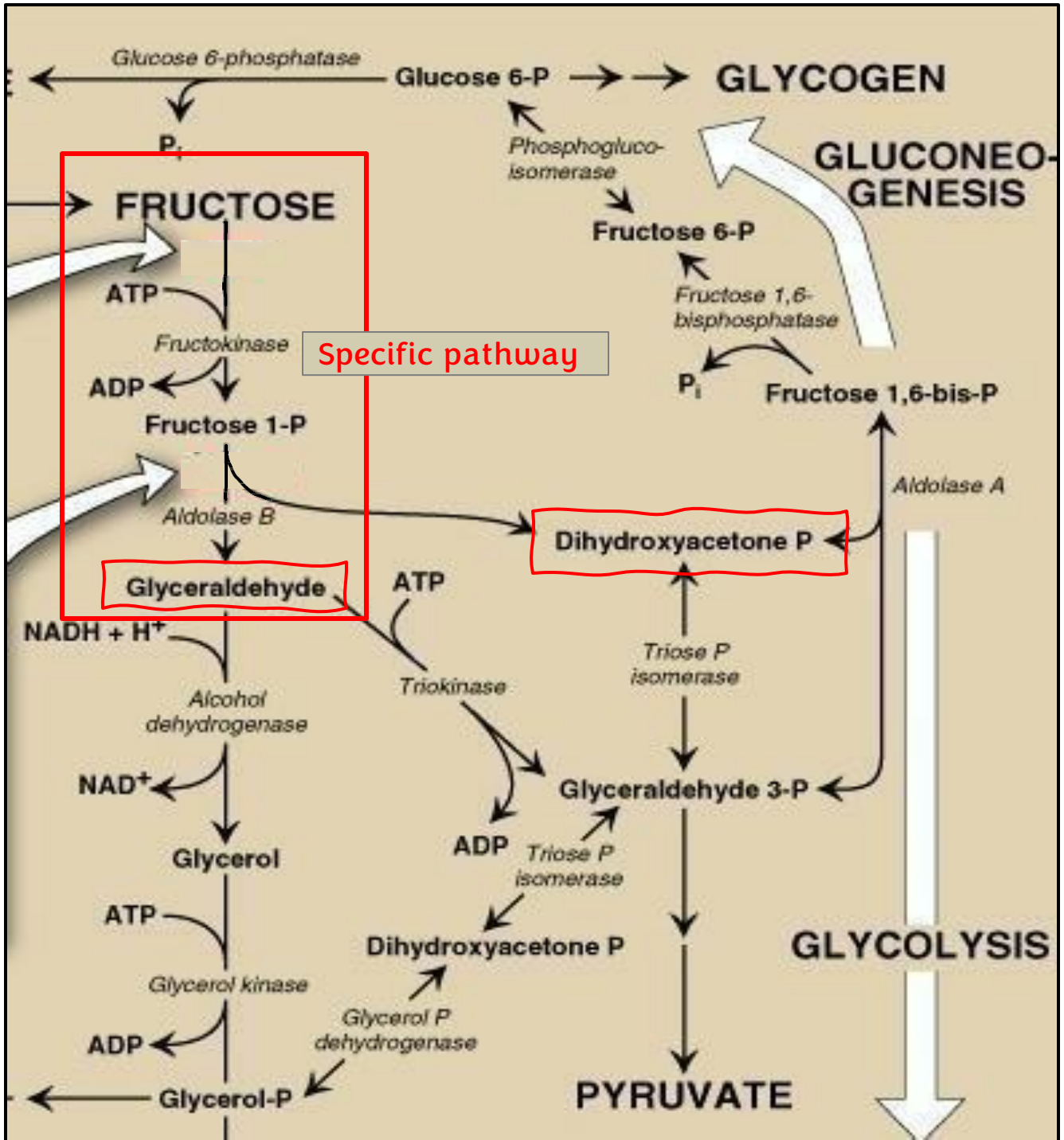
Aldolase A

- Works only in non-specific pathway.
- In most tissues.
- Substrate Fruc. 1,6 bisphospate Not Fruc. 1 phpsphate.

because it interacts with glycolysis.

↓activity➔ fructose intolerance

We will cover this later, but it is a condition where the body is unable to properly digest fructose, often leading to symptoms like bloating, abdominal pain, and diarrhea.



Fructose Metabolism and Interaction with other Pathways

For clarification, please refer to the next slide.

The **specific pathway** can interact with different metabolic pathways through its intermediates:

- **Dihydroxyacetone phosphate (DHAP)** can interact with both **gluconeogenesis** and **glycolysis etc.**

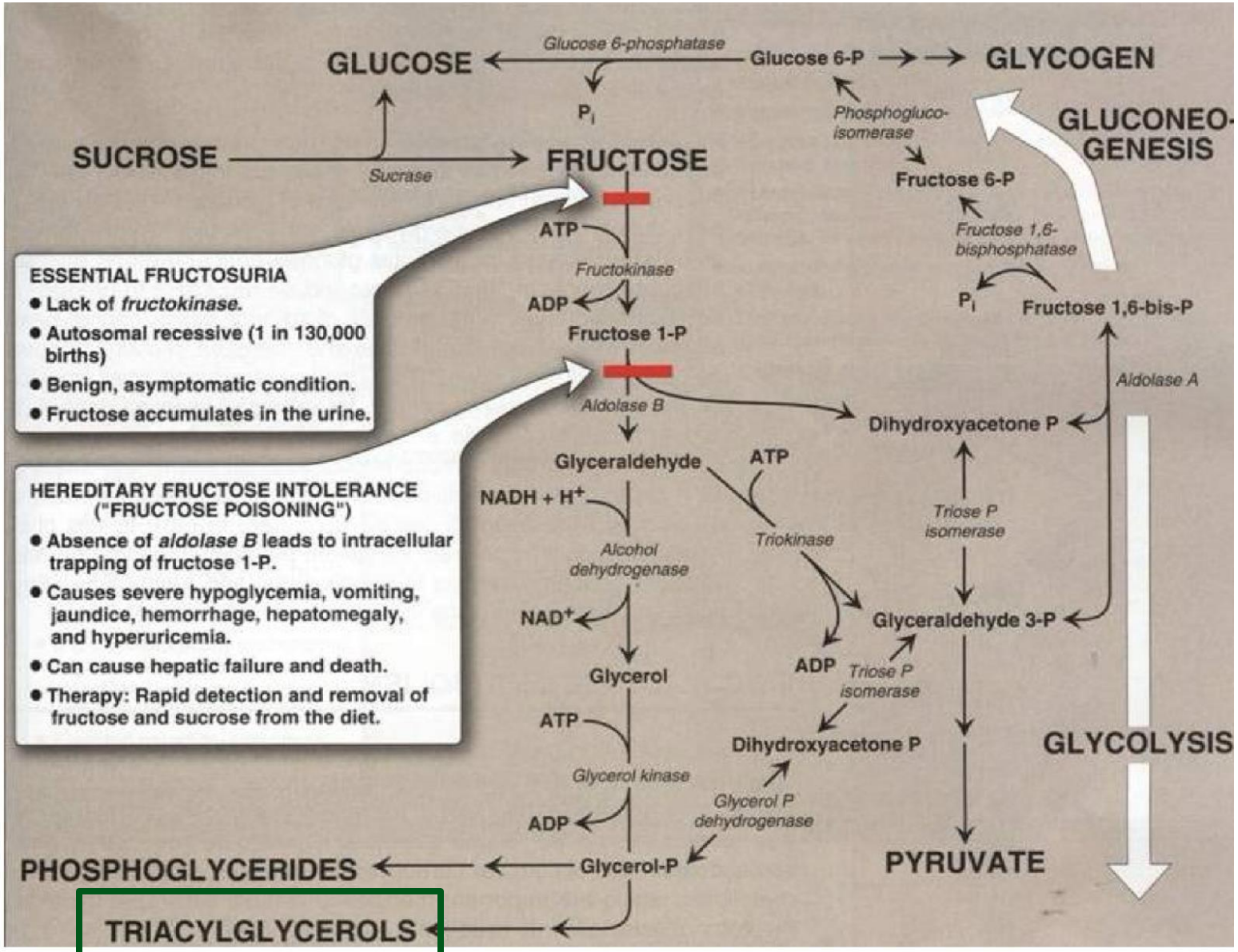
- **Glyceraldehyde** can be processed in two main ways:

1. Phosphorylation by triokinase using ATP to convert it to glyceraldehyde-3-phosphate, which then interacts with glycolysis or gluconeogenesis.

2. Alternatively, glyceraldehyde can undergo a **longer pathway**:

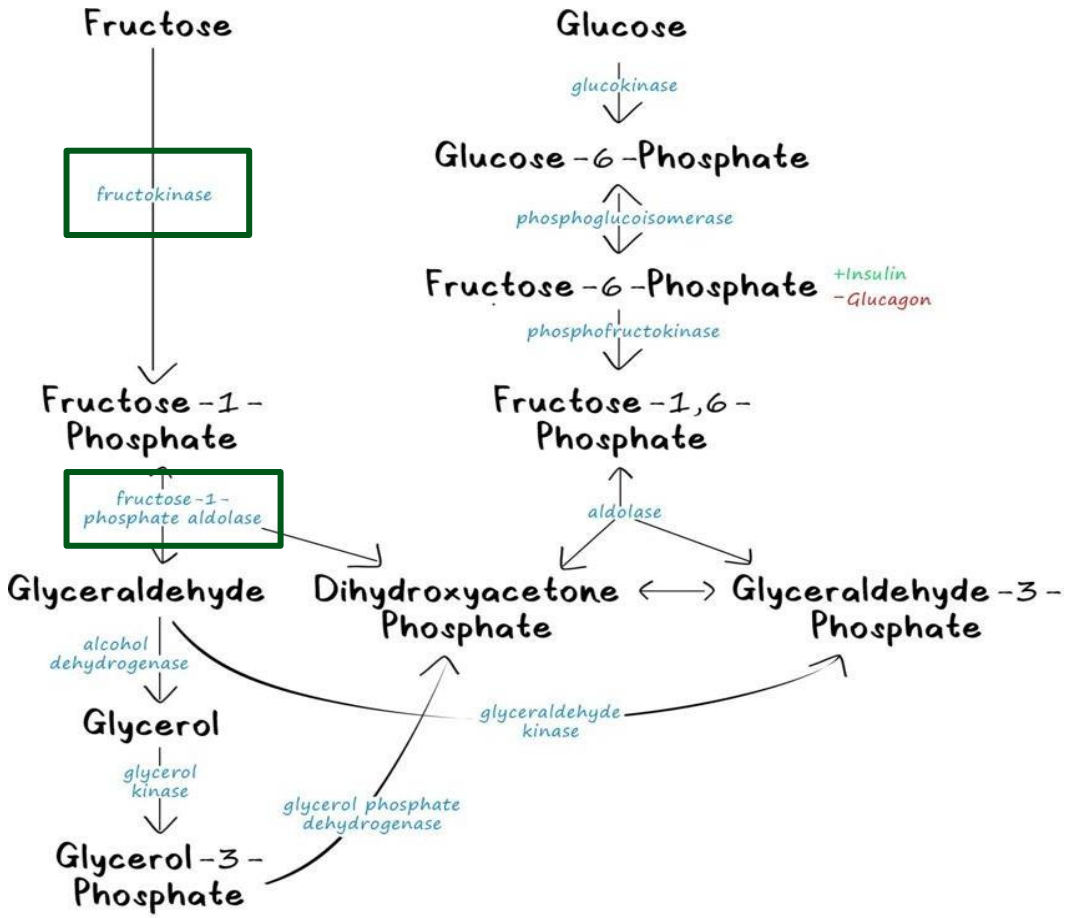
- First, it is reduced by **alcohol dehydrogenase** to form **glycerol**.
- Then, **glycerol** is phosphorylated by **glycerol kinase** to form **glycerol phosphate**, which is subsequently oxidized to **DHAP** and then isomerized to **G3P**.

3. Glyceraldehyde can also be used to build **triacylglycerols** (fats). That's why when you eat sugar, it can lead to weight gain, because it interacts with lipid synthesis promoting fat storage.


GLUCOSE
Glucose 6-phosphatase
Glucose 6-P
GLYCOGEN
P_i
Phosphogluco-isomerase
GLUCONEO-GENESIS
SUCROSE
Sucrase
FRUCTOSE
Fructose 6-P
ATP
Fructokinase
Fructose 1,6-bisphosphatase
ADP
P_i
Fructose 1,6-bis-P
Fructose 1-P
Aldolase A
Aldolase B
Dihydroxyacetone P
Glyceraldehyde
ATP
$NADH + H^+$
Triose P isomerase
Triokinase
Alcohol dehydrogenase
NAD^+
Glyceraldehyde 3-P
ADP
Triose P isomerase
Glycerol
ATP
Dihydroxyacetone P
GLYCOLYSIS
Glycerol kinase
Glycerol P dehydrogenase
ADP
PHOSPHOGLYCERIDES
Glycerol-P
PYRUVATE
TRIACYLGLYCEROLS
ESSENTIAL FRUCTOSURIA
• Lack of fructokinase.
• Autosomal recessive (1 in 130,000 births)
• Benign, asymptomatic condition.
• Fructose accumulates in the urine.
HEREDITARY FRUCTOSE INTOLERANCE ("FRUCTOSE POISONING")
• Absence of aldolase B leads to intracellular trapping of fructose 1-P.
• Causes severe hypoglycemia, vomiting, jaundice, hemorrhage, hepatomegaly, and hyperuricemia.
• Can cause hepatic failure and death.
• Therapy: Rapid detection and removal of fructose and sucrose from the diet.

Recap

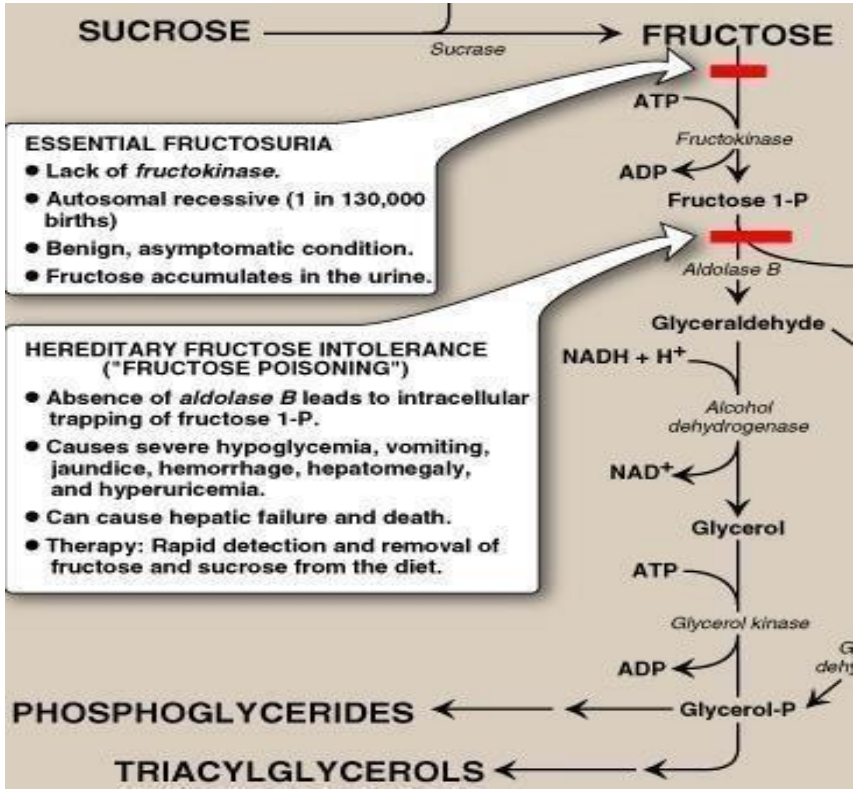
As previously mentioned, fructose may either be metabolized through a specific pathway, or a non-specific pathway. We discussed that the specific pathway is better because it skips the rate-limiting step (fructose 1,6-bisphosphate formation), thus saving time. The two important enzymes in the specific pathway of fructose metabolism are fructokinase and aldolase B. Fructokinase phosphorylates fructose into fructose 1- phosphate. Aldolase B catalyzes the cleavage of fructose-1-phosphate into two three-carbon intermediates, DHAP & glyceraldehyde.



Disorders of Fructose Metabolism

- Fructokinase Deficiency ➔ essential fructosuria Fructose appears in urine.
  - Accumulation of fructose ➔ fructosuria
  - Benign condition ⟶ We can use the alternative pathway.

Some accumulation of fructose could occur -> excreted in urine but it is not a big problem especially if the person reduced fructose in their diet.



- Aldolase Deficiency ➔ hereditary fructose intolerance, (Fructose Poisoning)
  - Severe disturbance in liver and kidney metabolism
  - ↑↑↑ Fruc. 1-Phosph. ➔ drop in P_i ➔drop in ATP ➔↑↑ AMP ➔ ↑ degradation of AMP
  - Hypoglycemia and lacticacidemia (lactic acidosis)
  - Hyperuricemia
  - Hepatic failure due to reduced hepatic ATP
  - Avoid fructose, sucrose and sorbitol ⟶ Sources of fructose

Explained in the next slide... :)

[]: concentration

Aldolase B Deficiency:

In the non-specific pathway, an aldolase B deficiency is not that devastating because aldolase A is present, and can cleave fructose-1,6-bisphosphate into DHAP and G3P, which can carry on to perform glycolysis. However, in the specific pathway where only aldolase B exists, a deficit in aldolase B causes fructose 1-phosphate to accumulate in the cell. Therefore, more ATP molecules are being broken down to supply inorganic phosphate with no subsequent outcomes. As a result, glycolysis is increasingly activated to compensate for the lost energy used for this phosphorylation. This causes **hypoglycemia and lacticacidemia,** which are both products of the increased [pyruvate], resulting in lactic acidosis.

Due to increased utilization of ATP, [AMP] will increase. AMP is a nucleotide, and adenine is a purine. We will learn later that the degradation of purines results in uric acid. AMP's accumulation in the cell leads to the activation of its degradation, causing **hyperuicemia.** Similarly, gout patients also have high [uric acid], due to either increased production, or decreased degradation.
Hepatic failure: the liver is a dynamic organ that needs energy; a decrease in hepatic ATP decreases gluconeogenesis and protein synthesis.

Additional Resources:

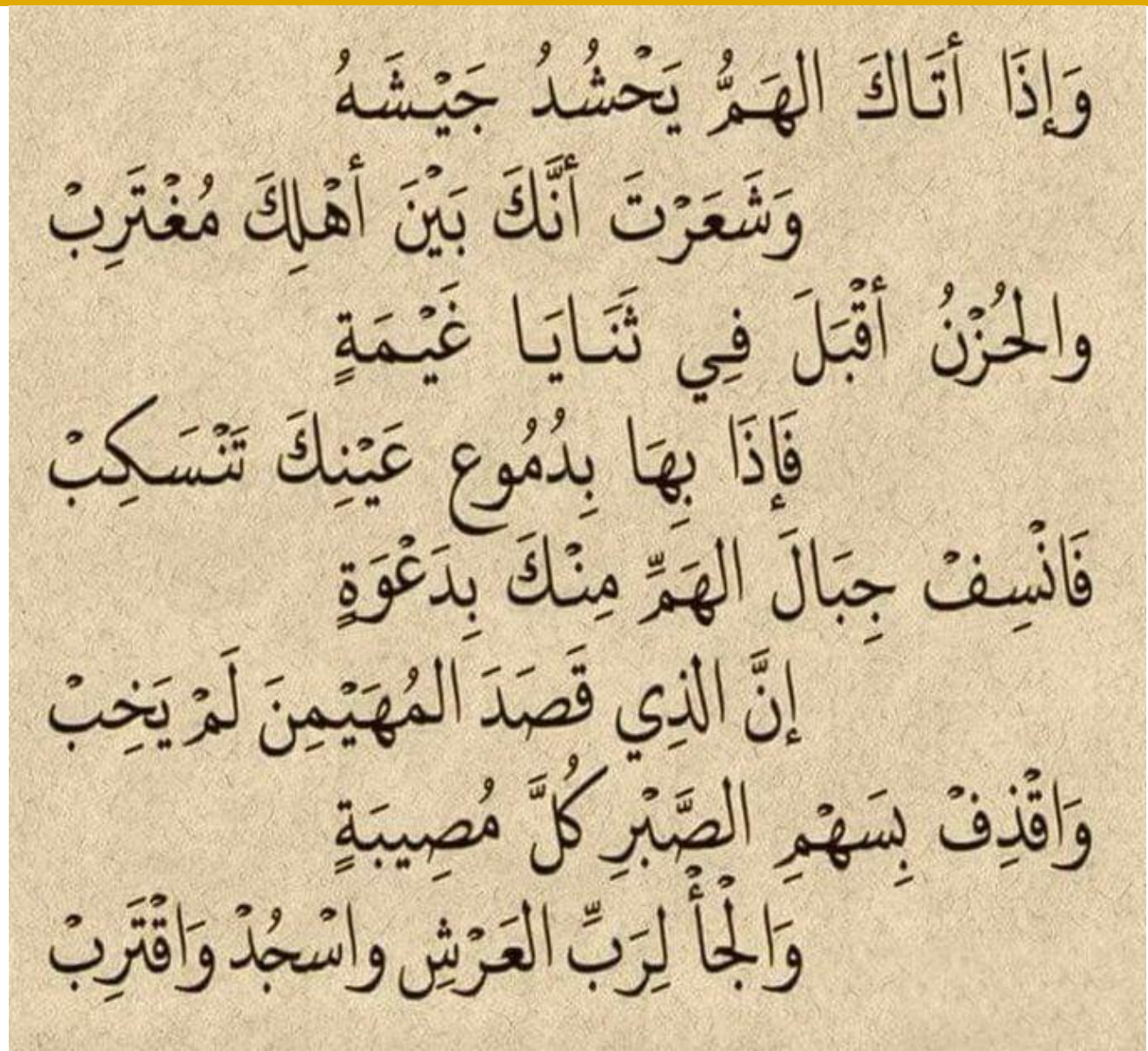
رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Lippincott Biochemistry 7th Ed. Chapter 12

Extra References for the Reader to Use:

1. Fructose Metabolism by Dirty Medicine YTV



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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			