METABOLISM OF FRUCTOSE:
Fructose is considered as an inverting sugar, because fructose is strongly levorotatory and changes (inverts) the weaker dextrorotatory action of Sucrose.

**SOURCES:**
1- Hydrolysis of Sucrose (by Sucrase).
2- Fruits & Honey.

**MAJOR PATHWAY:**

1- fructose + ATP \[\xrightarrow{\text{Fructokinase}}\] Frc-1-P + ADP

Fructokinase: (liver, kidney, intestines) is specific for fructose, not affected by feeding-fasting cycles nor by insulin levels, which may explain why fructose is cleared from the blood of diabetic patients at a normal rate.

Deficiency \[\Rightarrow\] leads to Essential fructosuria.

2- Frc1-P \[\xrightarrow{\text{Aldolase B}}\] DHAP + Glyceraldehyde

Aldolase B: is the cleavage enzyme, it’s found in and predominant in the liver, while aldolase A is found in all tissues.

Aldolase B deficiency \[\Rightarrow\] Hereditary fructose intolerance.
Increased Frc-1-P (pathological changes and high osmotic pressure)

Water retention

Jaundice, vomiting, hyperbilirubinemia and liver enlargement

This case occurs in infants after ablation, because the food given contains sucrose and this provides Fructose, the same symptoms are noticed and this
condition is called “Sequestering of phosphate”.

**Sequestering of phosphate:** phosphate is attached covalently to an inorganic molecule and is therefore no longer available to participate in other essential metabolic reactions.

\[ \downarrow \text{Pi} \rightarrow \downarrow \text{ATP from ADP + Pi} \text{ (especially in Liver which metabolites most dietary Fructose)} \]

![Fructose molecule](image)

(D-Fructose)

3- Interconversion of DHAP and Glyceraldehyde

☆ DHAP may be converted to Glycer. 3-P by an isomerase enzyme (See Glycolytic pathway).

☆ Glyceraldehyde may be phosphorylated to glyceraldehyde 3-P by ATP and a kinase enzyme → glycolysis & gluconeogenesis.
   or reduced to Glycerol → gluconeogenesis
   or oxidized to glycerate → serine biosynthesis.

**METABOLISM OF LACTOSE:**

A disaccharide of Glc and Galactose (Gal).

*Source:* milk biosynthesis in human “the mammary gland”.

1- UDP-Glc \( \xrightarrow{\text{epimerase}} \) UDP-Gal
UDP-Gal + D-Glucose $\xrightarrow{\text{Synthetase}}$ Lactose + UDP

$\alpha$-Lactalbumin (protein B)
+ $\beta$-D-Galtransferase (protein A)

UDP-Gal $\rightarrow$ Glycolipids, Glycoproteins & Glycosaminoglycans.

Prolactin: a hormone that increases the rate of synthesis of $\alpha$-lactalbumin $\rightarrow$ Lactose synthesis.

Protein B of the synthetase enzyme is abundantly found in milk.

2- Lactase (β-galactosidase) hydrolyzes lactose to glucose and galactose and is found in the small intestine. Its deficiency is called “alactasia”, results in Lactose intolerance which is either genetic or acquired disorder, its symptoms are diarrhea and flatus.

In infants, milk which is their primary food is not tolerable and lactose–free formula is used instead (Soya milk).
In adults, the condition is less serious and is treated by avoiding milk products.
Metabolism of Galactose:

1- \[ \text{Gal + ATP} \xrightarrow{\text{galactokinase}} \text{Gal-1-P + ADP} \]

Galactokinase Deficiency: it leads to Galactosemia and Galactosuria. In the lens of the eye, Gal is reduced to the sugar alcohol dulcitol (galactitol) by aldose reductase and causes an osmotic effect that lead to the development of Cataracts.

2- \[ \text{Gal-1-P} \xrightarrow{\text{4-epimerase}} \text{Glc-1-P} \]

Gal-1-P uridyl transferase deficiency \( \Rightarrow \) Classical Galactosemia.
Symptoms: Cataracts, mental retardation and liver cirrhosis.

3- UDP-Gal is converted to UDP-Glc by an Epimerase enzyme
4- epimerase deficiency \( \Rightarrow \) Galactosemia

Cases:
- Galactosemia: a male infant exhibits difficulty to feed, diarrhea, vomiting, and failure to thrive (grow). At 5 days of age, exhibits mild jaundice.
- Glycosuria: (Reducing sugar in urine) but not glucose, i.e. Galactosuria.
- Galactose-free diet: no milk is given, and for older people not even milk products.
- Glactose is important in Cerebrocytes, Brain & Cartilage.
- In case of milk deficiency in food, Gal can be synthesized in body by Glc-6-P \[ \xrightarrow{\text{UDP-Glc}} \text{UDP-Gal} \)
- \( \uparrow \text{Gal in Blood} \xrightarrow{\text{diffusion of Gal in Eye lens H}_2\text{reductase}} \text{Galactitol} \)

Galactitol is impermeable and accumulates in lens \( \uparrow \) osmotic pressure and \( \text{H}_2\text{O} \) retention \( \rightarrow \) Myopia; swelling of the eye and damage of lens tissue causing cataracts.

\( \bigstar \) Gal is necessary for milk lactose production in mammary gland. The process is done by the action of Galactosyl transferase enzyme which needs \( \alpha \)-lactoalbumin as a cofactor, this cofactor is synthesized in mammary gland in the last 3 months.
of pregnancy (i.e. 7th, 8th and 9th) when the progesterone level is decreased.

\[
\text{UDP-Gal + Glc} \xrightarrow{\text{Gal-transferase (protein A)}} \text{Lactose (normal in lactating mammary gland)}
\]

\[
\text{UDP-Gal + N-acetyl Glc N} \xrightarrow{\text{protein A}} \text{N-acetyl lactosamine (N-acetylgalactosamine)}
\]

Question:- Can lactose be synthesized directly from Glc?

Answer:- Yes,
Here’s how: Glc 6-P → UDP-Glc, by glycogenesis can be converted to UDP-Gal by isomerase enzyme, then UDP-Gal Forms lactose.

☆ Lactose synthase or synthetase (UDP-Gal: Glc galactosyl transferase) is composed of two proteins: A and B.

Hormonal control of lactose synthesis:
• Prior to and during pregnancy, the mammary gland synthesizes N-acetyl lactosamine.
  o During pregnancy, the steroid hormone, Progesterone inhibits the synthesis of protein B.
• After birth, progesterone levels drop significantly, stimulating the synthesis of the peptide hormone prolactin which in turn stimulates α-lactalbumin (protein B) synthesis. The resulting regulatory protein B forms a complex with the enzyme, protein A, changing the specificity of that transferase so that lactose, instead of N-acetyl lactosamine, is produced.

Ingestion of large quantities of fructose has profound metabolic consequences.

| Diets high in sucrose or in high-fructose Syrups (HFS) used in manufactured foods and beverages lead to large amounts of fructose (and glucose) entering the hepatic portal vein. |
Fructose undergoes more rapid glycolysis in the liver than does Glc, because it bypasses the regulatory step catalyzed by phosphofructokinase, this allows fructose to flood the pathways in the liver, leading to enhanced fatty acid synthesis, increased esterification of fatty acids and increased VLDL secretion, which may raise serum triacylglyceroles and ultimately raise LDL-cholesterol concentrations.

In extrahepatic tissues, HK catalyzes the phosphorylation of most hexose sugars, including fructose, but Glc inhibits the phosphorylation of fructose, since it’s a better substrate for HK. Nevertheless, some Frc. Can be metabolized in the adipose tissue and muscle. Fructose is found in seminal plasma. The presence of Sorbitol dehydrogenase in the liver, including the fetal liver, is responsible for the conversion of sorbitol into fructose. This pathway is also responsible for the occurrence of fructose in seminal fluid.
Large amounts of Glc enter these cells during times of hyperglycemia (uncontrolled D.M.)
Elevated Glc and adequate supply for NADPH → ↑Sorbitol, which can’t pass (trapped).

When Sorbitol dehydrogenase is low or absent, e.g: Kidney, lens, retina, nerve cells: Sorbitol accumulates → Strong osmotic effects → cell swelling (due to \( H_2O \) retention).
Some pathologic alterations associated with diabetes can be attributed to this phenomenon.

**Metabolism of Fructose**

- ⚠️ deficiency: 1) Deficiency of Fructokinase: leads to Essential Fructosuria.
  2) Deficiency of Aldolase B: leads to Hereditary Fructose Intolerance.

- ☯️: An enzyme called Sorbitol dehydrogenase
: note: DHAP & Glyceraldehyde 3P may be degraded by glycolysis or may be substrates for aldolase and hence glyconeogenesis, which is the fate of much of the fructose metabolized in the liver.

: HK = Hexokinase

: Aldolase A: found in all tissues.
  Aldolase B: Predominant in the liver.

: an enzyme called phosphotriose isomerase.