CARBOHYDRATE METABOLISM
DIGESTION & ABSORPTION

DIETARY CARBOHYDRATES

DIGESTION

MONOSACCHARIDE

DISACCHARIDES

POLYSACCHARIDE

Salivary α Amylase

MOUT

H

DEXTIN

STOMACH

NO DIGESTION

SMALL INTESTINE

Pancreatic α – amylase

MALTOSE

SUCROSE

LACTOSE

Maltase

Sucrase

Lactase

ABSORPTION

GLC

FRUC

GAL
Action of $\alpha$–amylase on glycogen:

Glycogen Molecule ($\alpha$, 1-4 bond, $\alpha$, 1-6 bond (branch point))

$\downarrow$

$\alpha$–amylase

Dextrin (oligosaccharide) + Maltotriose + Maltose + Isomaltose ($\alpha$, 1-6 bond)
## GLUCOSE TRANSPORTERS

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Present in</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glu T1</td>
<td>RBC, brain, kidney, colon, retina, placenta</td>
<td>Glucose uptake in most of the cells</td>
</tr>
<tr>
<td>Glu T2</td>
<td>Serosal surface of intestinal cells, liver, beta cells of pancreas</td>
<td>Low affinity; glucose uptake in liver, glucose sensor in beta cells</td>
</tr>
<tr>
<td>Glu T3</td>
<td>Neurons, brain</td>
<td>High affinity; glucose into brain cells</td>
</tr>
<tr>
<td>Transporter</td>
<td>Present in</td>
<td>Properties</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Glu T4</td>
<td>Skeletal, heart muscle, adipose tissue</td>
<td>Insulin mediated glucose uptake</td>
</tr>
<tr>
<td>Glu T5</td>
<td>Small intestine, testis, sperms, kidney</td>
<td>Fructose transporter; poor ability to transport glucose</td>
</tr>
<tr>
<td>Glu T7</td>
<td>Liver endoplasmic reticulum</td>
<td>Glucose from ER to cytoplasm</td>
</tr>
<tr>
<td>SGluT</td>
<td>Intestine, kidney</td>
<td>Cotransport; from lumen into cell</td>
</tr>
</tbody>
</table>
Glycolysis – Sequence of reactions converting glucose to pyruvate or lactate with the production of ATP. Also called as Embden-Meyerhof pathway (E.M. Pathway).

**Salient Features:**
1. Enzymes present in cytosol
2. Lactate is the end product under anaerobic condition and pyruvate is the end product under aerobic condition
3. Major pathway for ATP synthesis in tissues lacking mitochondria, e.g., erythrocytes, cornea, lens, etc.
4. Essential pathway in brain for energy
GLYCOLYSIS

1. Glucose + ATP → Glucose 6-phosphate + ADP
   - Hexokinase

2. Fructose 6-phosphate
   - Phosphohexose isomerase
   → Fructose 6-phosphate

3. Fructose 6-phosphate + ATP → Fructose 1,6-bisphosphate + ADP
   - Phosphofructokinase

4. Fructose 1,6-bisphosphate → Glyceraldehyde 3-phosphate + Dihydroxyacetone phosphate
   - Aldolase

5. Glyceraldehyde 3-phosphate + NAD → 1,3-bisphosphoglycerate + NADH + H^+
   - Glyceraldehyde 3-P DHase
   - Iodoacetate

6. 1,3-bisphosphoglycerate + ATP → 1,3-BPG Kinase
   → 1,3-bisphosphoglycerate + ADP

GLYCOLYSIS
3-phosphoglycerate

7 Phosphoglycerate mutase

2-phosphoglycerate

8 Enolase (Inhibitor = Fluoride)

Phosphoenol pyruvate

9 Pyruvate kinase

ADP

ATP

Pyruvate

10 Lactate Dehydrogenase

Lactate

Lactate Dehydrogenase

Pyruvate

Lactate

NADH + H^+  NAD^+
## Comparison of Hexokinase and Glucokinase

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Hexokinase</th>
<th>Glucokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In all tissues</td>
<td>Only in liver</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Km value</th>
<th>$10^{-2}$ mmol/L</th>
<th>20 mmol/L</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Affinity to substrate</th>
<th>High</th>
<th>Low</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Specificity</th>
<th>Acts on glucose, fructose &amp; mannose</th>
<th>Acts only on glucose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Induction</th>
<th>Not induced</th>
<th>Induced by insulin &amp; glucose</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Function</th>
<th>Even when blood sugar level is low, glucose is utilized</th>
<th>Acts when blood glucose level is $&gt;100$ mg/dl</th>
</tr>
</thead>
</table>
# REGULATION OF GLYCOLYSIS

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Activation</th>
<th>Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase</td>
<td>---</td>
<td>Glucose 6 phosphate</td>
</tr>
<tr>
<td>Glucokinase</td>
<td>Insulin</td>
<td>Glucagon</td>
</tr>
<tr>
<td>Phosphofructokinase</td>
<td>Insulin, AMP, Fructose, 6 phosphate, Phosphofructokinase-2, Fructose 2,6 bisphosphate</td>
<td>Glucagon, ATP, Citrate, Low pH, Cyclic AMP</td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td>Insulin, Fructose 1,6-bisphosphate</td>
<td>Glucagon, ATP, Cyclic AMP</td>
</tr>
<tr>
<td>Pyruvate Dehydrogenase</td>
<td>CoA, NAD⁺</td>
<td>Acetyl Co A, NADH</td>
</tr>
</tbody>
</table>
ENERGETICS (anaerobic condition)

<table>
<thead>
<tr>
<th>STEPS</th>
<th>ENZYMES</th>
<th>SOURCE</th>
<th>No. of ATPs gained per Glucose molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step – 1</td>
<td>Hexokinase</td>
<td>---</td>
<td>- 1</td>
</tr>
<tr>
<td>Step - 3</td>
<td>Phosphofructokinase</td>
<td>---</td>
<td>- 1</td>
</tr>
<tr>
<td>Step - 6</td>
<td>1,3-bisphosphoglycerate kinase</td>
<td>ATP</td>
<td>1 x 2 = 2&lt;br&gt;Total 4 – 2 = 2</td>
</tr>
<tr>
<td>Step - 9</td>
<td>Pyruvate kinase</td>
<td>ATP</td>
<td>1 x 2 = 2</td>
</tr>
</tbody>
</table>
## ENERGETICS (aerobic condition)

<table>
<thead>
<tr>
<th>STEP S</th>
<th>ENZYMES</th>
<th>SOURCE</th>
<th>No. of ATPs gained per Glucose molecule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step – 1</td>
<td>Hexokinase</td>
<td>---</td>
<td>- 1</td>
</tr>
<tr>
<td>Step – 3</td>
<td>Phosphofructokinase</td>
<td>---</td>
<td>- 1</td>
</tr>
<tr>
<td>Step - 5</td>
<td>Glyceraldehyde 3-phosphate dehydrogenase</td>
<td>NADH</td>
<td>$3 \times 2 = 6$</td>
</tr>
<tr>
<td>Step - 6</td>
<td>1,3, - bisphosphoglycerate kinase</td>
<td>ATP</td>
<td>$1 \times 2 = 2$</td>
</tr>
<tr>
<td>Step – 9</td>
<td>Pyruvate kinase</td>
<td>ATP</td>
<td>$1 \times 2 = 2$</td>
</tr>
</tbody>
</table>

**Total 10 – 2 = 8**
Rapaport Leubering Cycle (BPG Shunt):

GLYCERALDEHYDE 3-PHOSPHATE → GLUCOSE

1,3-BPG

Pi

NAD+

Glyceraldehyde 3-P Dehydrogenase

NADH+H+

BPG Mutase

2,3 BPG

ADP

ATP

3-PHOSPHOGLYCERATE

Pi

2,3 BPG Phosphatase

PYRUVATE
The 2,3-BPG combines with hemoglobin, and reduces the affinity towards oxygen. So, in the presence of 2,3-BPG, oxyhemoglobin will unload oxygen more easily in tissues.

Under hypoxic conditions the 2,3-BPG concentration in the RBC increases, thus favouring the release of oxygen to the tissues even when pO2 is low.

The compensatory increase in 2,3-BPG in high altitudes favours oxygen dissociation. BPG is increased in fetal circulation.

No ATP is generated.
Pyruvate to Acetyl CoA:
Pyruvate is converted to acetyl CoA by oxidative decarboxylation. This reaction is catalyzed by a multienzyme complex, pyruvate dehydrogenase (PDH) complex.
REGULATION OF PDH

PDH-a (Active)

PDH-b (Inactive)

Dichloroacetate

Pyruvate

Ca

ATP
ADP

Acetyl CoA/CoA

ATP/ADP

NADH/NAD

PDH Kinase

PDH Phosphatase

Pi

Mg, Ca

Insulin

+ + + +
CITRIC ACID CYCLE:

- The cycle was proposed by Sir Hans Krebs in 1937.
- It is the final common oxidative pathway that oxidizes acetyl CoA to CO2.
- It is the source of reduced co-enzymes that provide the substrate for the respiratory chain.
- It acts as a link between catabolic and anabolic pathways (amphibolic role).
- It provides precursors for synthesis of amino acids and nucleotides.
Acetyl-CoA + CoA-SH → Oxaloacetate

1- Citrate Synthase

NADH + H^+ + H_2O → 8- Malate Dehydrogenase

Malate + Aconitate → H_2O + 2- Aconitase

Malate Cis- + H_2O → 7- Fumarase

Fumarate + Isocitrate + H_2O → 6- Succinate DHase

Succinate + Fumarate + FADH_2 → 3- Isocitrate DHase

FAD + NADH + H^+ + GDP + Pi → GTP + NAD+ + CO_2 + CoA-SH

Succinyl CoA + Alpha ketoglutarate → 5- Succinate thiokinase

GTP + CoA-SH + NADH + H^+ + NAD+ + CO_2 + CoA-SH → 4- Alpha ketoglutarate DHase

CITRIC ACID CYCLE

D J
SIGNIFICANCE

1. Final common oxidative pathway
2. Complete oxidation of acetyl CoA
3. ATP generation
4. Integration of major metabolic pathways
5. Excess carbohydrates are converted as neutral fat
6. No net synthesis of carbohydrates from fat
7. Carbon skeletons of amino acids finally enter TCA cycle
8. Amphibolic pathway
9. Anaplerotic role of TCA cycle (replenish intermediate of TCA cycle)
# ATP Generating Steps:

<table>
<thead>
<tr>
<th>Step No</th>
<th>Reactions</th>
<th>Co-enzymes</th>
<th>ATPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Isocitrate to Alpha keto glutarate</td>
<td>NADH</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Alpha ketoglutarate to Succinyl CoA</td>
<td>NADH</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>Succinyl CoA to Succinate</td>
<td>GTP</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>Succinate to fumarate</td>
<td>FADH 2</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Malate to Oxaloacetate</td>
<td>NADH</td>
<td>3</td>
</tr>
</tbody>
</table>
Regulation

1. Citrate and Citrate Synthase:

- ATP acts as an allosteric inhibitor.
- Citrate allosterically inhibits PFK, the key enzyme of glycolysis; stimulates fructose 1,6,-bisphosphatase, a key enzyme of gluconeogenesis and activates acetyl CoA carboxylase, key enzyme of fatty acid synthesis.

2. Availability of ATP:

- The cycle is tightly coupled to the respiratory chain providing ATP.
- Anaerobiosis (hypoxia) will inhibit ETC, when NADH and FADH2 are accumulated, which in turn will cause inhibition of TCA cycle.
3. Isocitrate Dehydrogenase:

ADP acts as a positive modifier enhancing the binding of substrate. NADH is an inhibitor.

4. Alpha keto Glutarate Dehydrogenase:

It is inhibited by succinyl Co A and NADH.
INHIBITORS:

- **Aconitase** (citrate to aconitate) – It is inhibited by **fluoro-acetate** (Non-competitive inhibition)

- **Alpha keto glutarate dehydrogenase** (alpha keto glutarate to succinyl CoA) inhibited by **arsenite** (Non-competitive inhibition)

- **Succinate Dehydrogenase** (succinate to fumarate) inhibited by **malonate** (Competitive inhibition)
CORI’S CYCLE OR LACTIC ACID CYCLE

**BLOOD**

- Glucose
- Glycogen
- Lactate
- Pyruvate
- Alanine
- Urea

**LIVER**

- Glucose
- Glycogen
- Lactate
- Pyruvate
- Alanine
- Urea

**MUSCLE**

- Pyruvate
- Lactate
- Alanine
GLUCONEOGENESIS:

- It is a process by which glucose molecules are produced from non-carbohydrate precursors like glycerol, pyruvate, lactate and glucogenic aminoacids.
- Site: Liver; Organelle – mitochondrial & cytoplasmic.
- Key enzymes:

<table>
<thead>
<tr>
<th>Irreversible steps in glycolysis</th>
<th>Corresponding key gluconeogenic enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyruvate kinase (Step 9)</td>
<td>pyruvate carboxylase, phosphoenol pyruvate carboxy kinase</td>
</tr>
<tr>
<td>Phosphofructokinase (Step 3)</td>
<td>fructose 1,6-bisphosphatase</td>
</tr>
<tr>
<td>Hexokinase (Step 1)</td>
<td>glucose 6-phosphatase</td>
</tr>
</tbody>
</table>
Glucose $\xrightarrow{\text{Gl-6Pase}}$ Gl-6-F $\xrightarrow{\text{Hexokinase}}$ Glc-6-P $\xrightarrow{\text{Glycogen}}$ Fr-6-P

Fr-6-P $\xrightarrow{\text{Fr-1,6 BPase}}$ Fr 1,6-BP $\xrightarrow{\text{PFK}}$ Glyceraldehyde-3P $\xrightarrow{\text{ADP}}$ ATP $\xrightarrow{\text{NAD}}$ NADH + H$^+$

Glyceraldehyde-3P $\xrightarrow{\text{NAD}}$ DHAP

1,3-BPG $\xrightarrow{\text{ADP}}$ ATP

3-Phosphoglycerate $\xrightarrow{\text{AT}}$ Glycerol-3P $\xrightarrow{\text{GK}}$ Glycerol
GLUCOGENIC AMINO ACIDS

1. Glu, Arg, His, Pro, Gln
2. Met, Val, Ile
3. Phe, Tyr, Asp, Asn
4. Gly, Ala, Ser, Cys
SIGNIFICANCE

1. Only liver can replenish blood sugar through gluconeogenesis, because glucose 6-phosphatase is present mainly in liver.

2. During starvation gluconeogenesis maintains the blood glucose level.
   - Stored glycogen is depleted within first 12 – 18 Hrs of fasting
   - Prolonged starvation – gluconeogenesis (Source: glucogenic aminoacids from protein catabolism)
Energy Requirement:

- 2 pyruvate to 2 oxaloacetate = 2 ATP
- 2 oxaloacetate to 2 phosphoenol pyruvate = 2 ATP
- 2 X 3-phosphoglycerate to 2 X 1,3 – bisphospho glycerate = 2 ATP
- Total = 6 ATP

Glycolysis (generates 2 ATP)

Glucose → Lactate → Gluconeogenesis (utilises 6 ATP)
Substrates for Gluconeogenesis:

1. Lactate

2. Glucogenic amino acids

3. Glycerol

4. Propionyl CoA
Regulation of Gluconeogenesis:

- **Pyruvate Carboxylase**: It is an allosteric enzyme. Acetyl CoA is an activator of pyruvate carboxylase.

- **Fructose 1,6 bisphosphatase**: Citrate is an activator while fructose 2,6 bisphosphate and AMP are inhibitors

- **ATP**: Enhances the gluconeogenesis
Hormonal regulation:

(a) Glucagon and glucocorticoids increase gluconeogenesis

(b) Glucocorticoids induce the synthesis of hepatic amino transferases – provides substrate for gluconeogenesis

(c) High glucagon-insulin ratio also favours induction of synthesis of gluconeogenic enzymes (PEPCK, Fructose 1,6-bisphosphatase and glucose 6-phosphatase)

(d) Synthesis of glycolytic enzymes hexokinase, phosphofructokinase and pyruvate kinase are depressed

(e) Insulin inhibits the gluconeogenesis.
CLINICAL SIGNIFICANCE OF PYRUVATE METABOLISM

- **PYRUVATE CARBOXYLASE DEFICIENCY:**
  1. INBORN ERROR
  2. MENTAL RETARDATION
  3. 1 in 25,000 BIRTH
  4. LACTIC ACIDOSIS +

- **ETHANOL**: INHIBITS GLUCONEOGENESIS. DURING ETHANOL METABOLISM CYTOPLASMIC NADH IS INCREASED. PYRUVATE – MALATE – OXALOACETATE REACTIONS ARE REVERSED. EXCESSIVE INGESTION OF ALCOHOL ---- HYPOGLYCEMIA. NADH LEVEL↑ -- LACTATE ACCUMULATES
GLYCOGEN METABOLISM:

Glycogen is a homopolysaccharide with glucose units linked in alpha 1,4-linkages (straight line) and alpha 1,6-linkages (branching point). Branching makes the molecule more globular and less space-consuming

Functions:
- Storage form of carbohydrates in human (liver and muscle)
- Liver glycogen provides glucose during starvation
- Muscle glycogen acts as reserve fuel for muscle contraction

*All the enzymes related to glycogen are cytoplasmic
GLYCOGENESIS (Synthesis of Glycogen):

- Glucose
  - ATP
  - Glucokinase
  - ADP
  - Glucose 6-phosphate
  - Phosphoglucomutase
  - Glucose 1-phosphate
  - UTP
  - UDP glucose
  - pyrophosphorylase
  - PPI
  - UDP Glucose
(Glycogen primer)
glycogenin
Glycogen synthase
alpha 1,4 linkages
Branching Enzyme
glycogenin
Transfers 6 glucose residues to form a new branch
Alpha 1,6 linkage
glycogenin
Repeated action of glycogen synthase and branching enzyme
GLYCOGEN
GLYCOGENOLYSIS (Breakdown of Glycogen)

alpha 1,4-linkage

alpha 1,6-linkage

(alpha 1,4-linkage)

(Glycogen)

phosphate units released

Glu 1-phosphate sequentialy

Glycogen phosphorylase

(Limit Dextrin)

Action of glycogen phosphorylase stops

(transfer a trisaccharide to another branch)

Debranching enzyme (removes alpha 1,6 linkage) Glu unit/branching is released

Glycogen phosphorylase

Glu 1-phosphate units are released (Glucose 1-phosphate) sequentialy
DEBRANCHING ENZYME:

The branches of glycogen are cleaved by two enzyme activities present on a single polypeptide called debranching enzyme (bifunctional enzyme)

(1) Oligo alpha 1,4 – 1,4 glucan transferase: removes a fragment of three or four glucose residues attached at a branch and transfers them to another chain
(2) Amylo alpha 1,6 glucosidase: breaks alpha 1,6 bond and releases free glucose
REGULATION OF GLYCOGEN METABOLISM:
cAMP mediated activation cascade

Epinephrine/Glucagon

Adenylyl cyclase (in cell membrane)

ATP $\rightarrow$ cAMP $\rightarrow$

Inactive Protein Kinase $\rightarrow$ P

Phosphorylase kinase

Phosphorylase kinase (inactive/dephosphorylated) (active/phosphorylated)

Glycogen synthase (active/dephosphorylated)

Glycogen synthase (inactive/phosphorylated)

Glycogenesis is inhibited
## Glycogen Storage Disease (Glycogenosis):

<table>
<thead>
<tr>
<th>Type</th>
<th>Name</th>
<th>Enzyme deficient</th>
<th>Primary organ involved</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Von Gierke’s Disease</td>
<td>glucose 6-phosphatase</td>
<td>Liver, kidney</td>
<td>Fasting hypoglycemia, hepatomegaly</td>
</tr>
<tr>
<td>II</td>
<td>Pompe’s Disease</td>
<td>Lysosomal maltase</td>
<td>organs with lysosomes</td>
<td>Liver, heart and muscle affected; death before 2 yrs</td>
</tr>
<tr>
<td>III</td>
<td>Cori’s Disease</td>
<td>Debranching enzyme</td>
<td>Liver, skeletal muscle, heart</td>
<td>Highly branched dextrin accumulates; hepatomegaly</td>
</tr>
<tr>
<td>IV</td>
<td>Anderson’s Disease</td>
<td>Branching enzyme</td>
<td>Liver</td>
<td>Glycogen with few branches; hepatomegaly</td>
</tr>
<tr>
<td>V</td>
<td>McArdle's Disease</td>
<td>Muscle phosphorylase</td>
<td>Skeletal muscle</td>
<td>Exercise intolerance</td>
</tr>
<tr>
<td>VI</td>
<td>Her’s Disease</td>
<td>Liver phosphorylase</td>
<td>Liver</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>VII</td>
<td>Tarui’s Disease</td>
<td>Muscle PFK</td>
<td>Muscle &amp; RBC</td>
<td>Accumulation of glycogen in muscles</td>
</tr>
<tr>
<td>VIII</td>
<td></td>
<td>Liver phosphorylase kinase</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td>Lewis Disease</td>
<td>Glycogen synthase</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Regulation of HMP Shunt:

- The pathway is regulated by NADP⁺.
- Step 1 catalyzed by GPD is the rate limiting step and is inhibited by NADPH.
- Oxidative phase is controlled by the level of NADP⁺.
- Non-oxidative phase is controlled by the requirement of pentoses.
- Insulin induces GPD.

Physiological Significance of the pathway:

1. Pathway is operating in following organs:
   
   (a) Liver
   (b) Adipose tissue
   (c) Adrenal Cortex
   (d) Mammary glands
   (e) Testes and ovaries
   (f) RBCs
   (g) Lens of eye

2. Generation of Reducing Equivalents:

   The major metabolic role of the pathway is to provide cytoplasmic NADPH for reductive biosynthesis of fatty acids, cholesterol and steroids.
3. Free Radical Scavenging:

- Free radicals (super oxide, hydrogen peroxide) are continuously produced in all cells.
- They destroy DNA, proteins, fatty acids and all biomolecules.
GALACTOSE METABOLISM:

1. Galactokinase
   2. Galactose 1-phosphate uridyl transferase

Clinical Significance:
- Galactosemia
- Galactokinase deficiency

Reactions:
1. Galactose + Mg++ $\rightarrow$ Galactose 1-phosphate
2. Glucose 1-phosphate $\rightarrow$ UDP Glucose + ATP
3. UDP Glucose + ADP $\rightarrow$ UDP Galactose + P Pi
4. UDP Galactose $\rightarrow$ UTP

Compounds:
- Galactose
- Galactose 1-phosphate
- UDP Glucose
- ATP
- ADP
- P Pi
- UTP
GLUCURONIC ACID PATHWAY:

Importance:

- It provides UDP-glucuronic acid, which is the active form of glucuronic acid. It is used for
  1. Conjugation of bilirubin
  2. Conjugation of steroids
  3. Conjugation of drugs
  4. Synthesis of glycosaminogycans (GAG)
- Barbiturates, antipyrine and aminopyrine will increase the uronic acid pathway, leading to availability of more glucuronate for conjugation purpose
- The enzyme L-gulonolactone oxidase is absent in human beings, primates, guinea pigs and bats. Hence ascorbic acid cannot be synthesized by these organisms. Hence, ascorbic acid becomes essential in diet for human beings
Glucuronic acid pathway:

- **UDPG-dehydrogenase**
  - UDP-glucose → UDP-glucuronic acid
  - 2NAD$^+$ → 2NADH$+H^+$

- **Glucuronidase**

- **Glucuronate reductase**
  - UDP-glucuronate → L-gulonate
  - NADP$^+$ → NADPH$+H^+$
  - H$_2$O

- **Gulonolactone oxidase**
  - L-gulonolactone → 2-keto L-gulonolactone
  - NADPH$+H^+$

- **Gulonate oxidase**
  - 2-keto L-gulonolactone → 3-keto L-gulonate
  - L-xylulose

- Ascorbic acid
- Spontaneous
  - (in lower animals)

- Block in primates
- CO$_2$
Essential Pentosuria

D-xylulose

D-xylulose – 5-phosphate

Pentose phosphate pathway

CLINICAL CONDITION: Essential Pentosuria
The amino sugars, N-acetyl glucosamine, N-acetyl galactosamine and N-acetyl neuraminic acid are synthesized from fructose-6 phosphate.

The amino group is derived from amide group of glutamine.

The reaction is catalyzed by an amido transferase – a irreversible and a rate-limiting step.
SYNTHESIS OF N-ACETYL NEURAMINIC ACID (NANA):

N-acetyl glucosamine \(\rightarrow\) N-acetyl mannosamine

ATP \(\rightarrow\) ADP

mannosamine 1-phosphate

Mutase

mannosamine 6-phosphate

+ Phosphoenol pyruvate

Aldolase enzyme

acid 9-phosphate

N-acetyl neuraminic acid
**FRUCTOSE METABOLISM:**

Glycogen

\[
\text{Hexokinase} \quad \text{NADP}^+ \quad \text{NADPH}+\text{H}^+ \quad \text{Glucose} \quad \text{Fructose} \quad \text{Hexokinase} \quad \text{Fructose 6-phosphate} \quad \text{Fructokinase} \quad \text{PFK} \quad \text{Fructose 1,6-bisphosphatase} \quad \text{DHAP} \quad \text{DHAP} \\
\text{Sorbitol} \quad \text{Aldose reductase} \quad \text{Glucose 6-phosphate} \quad \text{Phosphohexose isomerase} \quad \text{NAD}^+ \quad \text{Sorbitol DHase} \quad \text{NADH}+\text{H}^+ \quad \text{Fructose 1-phosphate} \quad \text{Glycerol} \quad \text{Glycerol kinase} \quad \text{Glycerol 3 Phosphate} \quad \text{Glycerol 3 P DHase} \quad \text{DHAP} \\
\text{Glucose 6-phosphatase} \quad \text{Fructose 6-phosphate} \quad \text{Triokinase} \quad \text{ATP} \quad \text{Triose phosphate isomerase} \quad \text{Alcohol DHase} \quad \text{Gly 3 P} \quad \text{D} \quad \text{J} \quad \text{Glycerol} \quad \text{Glycerol kinase} \quad \text{Glycerol 3 Phosphate} \quad \text{Glycerol 3 P DHase} \quad \text{DHAP} \]
POLYOL PATHWAY OF GLUCOSE:

- Sorbitol is poorly absorbed from intestine. It involves the reduction of glucose by aldose reductase to sorbitol, which can then be oxidised to fructose.

- Sorbitol is normally present in lens of eyes. But in diabetes mellitus, when glucose level is high, the sorbitol concentration also increases in the lens. This leads to osmotic damage of the tissue and development of cataract.

\[
\text{Glucose} \rightarrow \text{NADPH} + \text{H}^+ \rightarrow \text{Aldose reductase} \rightarrow \text{NADP}^+ \rightarrow \text{Sorbitol} \rightarrow \text{NAD}^+ \rightarrow \text{Sorbitol dehydrogenase} \rightarrow \text{NADH}^+ \rightarrow \text{Fructose}
\]
ALCOHOL METABOLISM:

Ethanol $\rightarrow$ NAD$^+$

Alcohol $\rightarrow$ NADH + H$^+$

Acetaldehyde $\rightarrow$ NAD$^+$

Aldehyde $\rightarrow$ NADH + H$^+$

Acetic acid
Biochemical alterations of Alcoholism:

Both the oxidation steps of alcohol produces NADH, resulting in a high NADH / NAD\(^+\) ratio. As a result the following metabolic adaptations occur,

- Lactic acidosis
- Hypoglycemia
- Ketogenesis
- Fatty liver
- CNS depression

Chronic Alcoholism:

(a) Alcoholism and Liver – accumulation of fat in liver cells leading to fatty liver; fibrosis of liver (cirrhosis) also takes place

(b) Alcoholism and Nervous System – Wernick’s disease

(c) Alcohol and CVS – myocardial infarction
LACTOSE INTOLERANCE:

- Lactase hydrolyses lactose to glucose and galactose

- Lactase is present in brush border of enterocytes

- Deficiency of lactase leads to lactose intolerance. In this condition, lactose accumulates in the gut. Irritant diarrhoea and flatulence are seen

- Acquired lactose intolerance – sudden change into a milk based diet. Lactase is an Inducible enzyme. If milk is withdrawn temporarily, the diarrhoea will be limited. Curd is an effective treatment, because the lactobacilli present in curd contains the enzyme lactase
REGULATION OF BLOOD GLUCOSE

Hyperglycemic Factors
(Sources of Blood Glucose)

Absorption from GIT

Glycogenolysis in liver

PLASMA GLUCOSE
Fasting: 70 – 110 mg/dl
Post-prandial: <140 mg/dl

Gluconeogenesis in liver

Hypoglycemic Factors
(Factors removing glucose from blood)

Glycolysis & TCA Cycle

Glycogen Synthesis in liver

Lipogenesis

Glucagon / Adrenaline
Corticosteroids
Growth hormone
ACTH, Thyroxine

INSULIN
Post-prandial Regulation

- Following a meal, glucose is absorbed from the intestine and enters the blood.

- Glucose stimulates the secretion of insulin by beta cells of islets of Langerhans of pancreas.

- The uptake of glucose by most extrahepatic tissues, except brain is dependent on insulin.

- Insulin helps in the storage of glucose as glycogen or its conversion to fat.
Fasting Regulation:

- Normally after 2 to 2 ½ hours after a meal, the blood glucose level falls to near fasting levels. The further fall is prevented by the processes that contribute glucose to the blood.

- For another 3 hours, hepatic glycogenolysis will take care of the blood sugar level.

- Thereafter, gluconeogenesis will take charge of the situation.

- Liver is the major organ that supplies the glucose for maintaining blood glucose level.

- Anti-insulin hormones or hyperglycemic hormones like glucagon, epinephrine, glucocorticoids, growth hormone, ACTH and thyroxine will keep the blood glucose level from falling.
BLOOD GLUCOSE REGULATION DURING FASTING (HIGH GLUCAGON).

LIVER
(GLYCOGENOLYSIS, GLUCONEOGENESIS)

(+)

GLUCOSE

LIPOGENESIS

MUSCLE

FFA

LIPOLYSIS

INTESTINE

ADIPOSE TISSUE
BLOOD GLUCOSE REGULATION DURING POST-PRANDIAL STATE (HIGH INSULIN).
Normal Plasma Levels:

**Fasting** plasma glucose value is **70 – 110 mg/dl**

Normal blood glucose level = 
Normoglycemia

Increased blood glucose level = 
Hyperglycemia

Decreased blood glucose level = 
Hypoglycemia

Sugar in Urine:

Normal - No excretion of sugar

180 mg/dL - Renal Threshold value for Glucose

> 180 mg/dL - Glycosuria
EFFECTS OF HORMONES ON GLUCOSE LEVEL IN BLOOD:

A. Insulin (hypoglycemic hormone)
   1. Lowers blood glucose
   2. Favors glycogen synthesis
   3. Promotes glycolysis
   4. Inhibits gluconeogenesis

B. Glucagon (Hyperglycemic hormone)
   1. Increases blood glucose
   2. Promotes glycogenolysis
   3. Enhances gluconeogenesis
   4. Depresses glycogen synthesis
   5. Inhibits glycolysis
C. Cortisol (Hyperglycemic Hormone)
1. Increases blood glucose level
2. Increases gluconeogenesis
3. Releases amino acids from the muscle

D. Epinephrine or Adrenaline (Hyperglycemic Hormone)
1. Increases blood sugar level
2. Promotes glycogenolysis
3. Increases gluconeogenesis
4. Favours uptake of amino acids

E. Growth Hormone (Hyperglycemic Hormone)
1. Increases blood sugar level
2. Decreases glycolysis
3. Mobilizes FA from adipose tissue
Determination of Glucose in body Fluids:

- The blood is collected using anticoagulant (potassium oxalate)

- inhibitor of glycolysis - Sodium Fluoride

- Capillary blood from finger tips used for glucose estimation by strip method

- Enzymatic Method: GOD-POD – Glucose Oxidase Method

- Glucometer-Less accurate
GTT:

A well standardized test and is highly useful to diagnose diabetes mellitus in doubtful cases

Indications for OGTT:

Patient has symptoms suggestive of diabetes mellitus; but fasting blood sugar value is inconclusive (between 110 to 126 mg/dl)

During pregnancy, excessive weight gaining is noticed, with a past history of big baby (more than 4 Kg) or a past history of miscarriage

To rule out benign renal glucosuria
Preparation of the Patient:

The patient is instructed to have good carbohydrate diet for 3 days prior to the test.

The diet containing about 30 – 50 g of carbohydrate should be taken on the evening prior to the test.

Patient should avoid drugs likely to influence the blood glucose levels, for atleast 2 days prior to the test.

Patient should abstain from smoking during the test.

Strenuous exercise on the previous day is to be avoided

Patient should not take food after 8 PM the previous night and not to take any breakfast to ensure 12 hours fasting.
Conducting GTT:

At about 8 AM, fasting blood and urine sample is collected

75 g anhydrous glucose in 250 to 300 ml of water is given orally (within 5 mins)

Sample Collection: The blood and urine samples are collected every ½ an hour
• Glucose tolerance test or GTT is a well-standardized test, highly useful to diagnose doubtful cases of diabetes mellitus.

• **Types:**
  I. Oral
  II. I.V.
INDICATIONS FOR OGGT

• Patient has symptoms suggestive of DM, but FBS value is inconclusive (between 100 & 126 mg/dl)

• In pregnancy, in case of excessive weight gain, past h/o big baby or miscarriage.

• To rule out benign renal glycosuria.
CONTRAINDICATIONS

• Cases of confirmed DM.

• Acutely ill patients.

• Follow-up of diabetes.
PREPARATION OF PATIENT

• Patient is instructed to have good carbohydrate diet (>150 g carbohydrate) for 3 days prior to test. Diet of 30-50 g carbohydrate has to be taken on evening prior to the test.
• Avoidance of hypoglycemic drugs for previous 2 days.
• Avoidance of strenuous exercise.
• 12 hours fasting prior to test.
• Abstain from smoking during test.
• Comfortable seated posture.
• Sample of blood and urine to be collected at fasting stage.
FACTORS AFFECTING GTT

• Insulin level
• Carbohydrate starvation
• Exercise
• Liver disease
• Acute infections
• Thiamine deficiency
• Thyroid disorders
GLUCOSE LOAD
DOSE

• 75 gm anhydrous glucose in 250-300 ml water is standard dose. To be given over a period of 5 minutes.

• Children: 1.75g/kg body weight.

• Pregnant: 100 gm anhydrous glucose.
SAMPLE COLLECTION

• Blood and urine samples collected at ½ hr interval for next 2½ hrs.

• Total 6 samples including 0-hr sample.

• Glucose is estimated in all blood samples.

• Urine samples tested qualitatively for presence of glucose.
MINI-GTT

• According to present WHO recommendation, collection done only at 0-hr and 2-hr post glucose load.
GTT IN PREGNANCY

• 100 gm anhydrous glucose load.

• Blood and urine samples to be collected at 0,1,2,3 hours respectively.
NORMAL VALUES

• Fasting plasma sugar: 70-110 mg/dl.
• Peak level reaches at 1 hr after glucose load.
• Comes down to normal by 2 to 2¹/² hrs due to insulin action in response to glucose dose.
• No urine sample contain glucose.
NORMAL GTT CURVE
## PBS IN OGTT IN NORMAL & DIABETICS (WHO1999)

<table>
<thead>
<tr>
<th></th>
<th>NORMAL</th>
<th>DM</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBS</strong></td>
<td>&lt;110mg/dL</td>
<td>&gt;126 mg/dL</td>
<td>&gt;110 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;6.1 mmol/L</td>
<td>&gt;7.0 mmol/L</td>
<td>&lt;126 mg/dL</td>
</tr>
<tr>
<td>1 hr PPB S</td>
<td>&lt;160 mg/dL</td>
<td>Not prescribed</td>
<td>Not prescribed</td>
</tr>
<tr>
<td></td>
<td>&lt;9.0 mmol/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 hr PPB S</td>
<td>&lt;140 mg/dL</td>
<td>&gt;200 mg/dL</td>
<td>&gt;140 mg/dL</td>
</tr>
<tr>
<td></td>
<td>&lt;7.8 mmol/L</td>
<td>&gt;11.1 mmol/L</td>
<td>&lt;200 mg/dL</td>
</tr>
</tbody>
</table>
GTT CURVE

RENAL THRESHOLD

DM

IMPAIRED

NORMAL
CAUSES FOR ABNORMAL GTT CURVE

• GDM

• Alimentary glycosuria

• Flat GTT

• Renal glycosuria
GDM

- FBS >126 mg/dl.

- H/O big baby or BOH.

- Women with GDM are at risk of developing frank diabetes.

- Known diabetic mother is not under this category.
ALIMENTARY GLYCOSURIA

- FBS & PPBS normal; exaggerated rise following glucose load is seen.
- Occurs due to ↑intestinal absorption of glucose.
- One or two urine samples may be positive for Benedict’s test.
- Occur following a period of deficient carbohydrate intake, after gastrectomy, in hyperthyroidism: Reactive hypoglycemia due to exaggerated insulin secretion.
ALIMENTARY GLYCOSURIA

RENAL THRESHOLD

![Graph showing alimentary glycosuria with renal threshold](image-url)
FLAT GTT GRAPH

- Malabsorption
- Addison’s disease
- Hypopituitarism
- Hypothyroidism
RENEAL GLYCOSURIA

• Lowering of renal threshold (normal = 180mg/dl).
• GLUT2 transporter defective.
• Physiological: Pregnancy
• Pathological: Renal tubular transport defect in Fanconi’s syndrome
I.V. GTT

- 0.5 g/kg wt (max 35 g) glucose in 100 ml sterile water given i.v. within 3 minutes
- Mid injection time is “0” time
- Blood samples collected at 10 min interval for next hour
- Peak value reached within a few minutes (200-250 mg/dl)
- In normal, value starts to reduce by 20-30 min, reaches 100 mg/dl by 45-60 min
- No. of minutes taken to reduce pbs level to half of peak value: $t_{1/2}$
- $t_{1/2} < 45$ in normal & $> 60$ in DM
CORTICOSTEROID STRESSED GTT

• Cortisone (100 mg) in 2 divided doses given orally
• Then Glucose given orally.
• Normal PBS at 1 hr < 180 mg/dl
  at 2 hr < 160 mg/dl
• High value in diabetes prone patients
DIABETES MELLITUS:

Diabetes mellitus is a metabolic disease due to absolute or insulin deficiency.

1. Type 1 Diabetes Mellitus:

   (Insulin Dependent Diabetes Mellitus - IDDM)

In this condition circulating insulin level is deficient

About 5% of total diabetic patients are of type 1

a. Immune mediated

b. Idiopathic

Decreased insulin production, hence circulating level is low, these patients dependent on insulin injection

Onset is usually below 30 years

They are more prone to develop ketosis

An autoimmune basis is attributed to most of these cases

Circulating antibodies against insulin is seen in 50% of cases and antibodies against islet cell cytoplasmic proteins are seen in 80% of cases
2. Type 2 Diabetes Mellitus

- Non-insulin Dependent Diabetes Mellitus - NIDDM
- Circulating insulin level is normal or mildly elevated or slightly decreased, depending on the stage of the disease
- 95% of patients belong to this type
- Disease is due to decreased biological response to insulin – insulin resistance, so there is relative insulin deficiency
- Seen in individuals above 40 years
- These patients are less prone to develop ketosis
- About 60% of patients are obese
- These patients have high plasma insulin levels
- Maturity onset diabetes of young (MODY) is due to defective glucokinase
- This mutation produces relative insulin deficiency by increasing the threshold for glucose induced insulin secretion
Classification:
(a) Obese
(b) Non-obese
(c) Maturity onset Diabetes of young (MODY)

3. Diabetic Prone States
(a) Gestational Diabetes Mellitus (GDM)
(b) Impaired Glucose Tolerance (IGT)
(c) Impaired Fasting Glycemic (IFG)

4. Secondary to other known causes
(a) Endocrinopathies (Cushing’s Disease, Thyrotoxicosis, Acromegaly)
(b) Drug-induced (Steroids, beta-blockers)
(c) Pancreatic Diseases (Chronic pancreatitis, fibrocalculus pancreatitis, hemochromatosis, cystic fibrosis)
<table>
<thead>
<tr>
<th>METABOLISM</th>
<th>KEY ENZYME</th>
<th>INSULIN ACTION ON ENZYME</th>
<th>DIRECT EFFECT</th>
<th>OVERALL EFFECT</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate</td>
<td>Translocase, Glucokinase, PFK, PK</td>
<td>Stimulation</td>
<td>Glycolysis favoured</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Pyruvate carboxylase, PEPCK, Fructose 1,6-bisphosphatase, Glucose 6-phosphatase, Glycogen synthase, Glycogen phosphorylase GPD</td>
<td>Inhibition Activation Inactivation Stimulation</td>
<td>Gluconeogenesis depressed Glycogen deposition Glycogen deposition</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Lipid</td>
<td>Acetyl CoA carboxylase, GK Hormone sensitive lipase HMG CoA reductase</td>
<td>Stimulation Stimulation Inhibition Stimulation</td>
<td>Lipogenesis favoured Lipolysis inhibited Cholesterol synthesis</td>
<td>Lipogenesis Decreased ketogenesis</td>
</tr>
<tr>
<td>METABOLISM</td>
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</tr>
<tr>
<td></td>
<td>Transaminase Ornithine transcarbamoylase RNA polymerase &amp; ribosome assembly</td>
<td>Inhibition</td>
<td>Catabolism inhibited Protein synthesis favoured</td>
<td>General anabolism</td>
</tr>
</tbody>
</table>
Clinical Presentations in Diabetes Mellitus:

- Glucosuria
- Polyuria
- Polydypsia
- Polyphagia
- Loss of weight

Acute Metabolic Complications:

(a) Diabetic Ketoacidosis

- More common in type 1 DM

- As oxaloacetate is diverted for gluconeogenesis, the TCA cycle cannot consume all the acetyl CoA. Hence more acetyl CoA is converted to ketone bodies. This leads to ketone bodies in blood (ketonemia)

- The presence of ketone bodies in urine (ketonuria) is detected by Rothera’s test. The accumulation of ketone bodies (acetoacetate and beta hydroxy butyrate) lowers the plasma pH. So, metabolic acidosis occurs. This condition is called diabetic ketoacidosis
(b) Hyperosmolar nonketotic coma:

This results in the elevation of glucose to very high levels (900 mg/dl or more). This increases the osmolality of ECF. Osmotic diuresis leads to water and electrolyte depletion. The coma results for dehydration of cerebral cells due to hypertonicity of ECF.

Chronic complications of Diabetes Mellitus:

Vascular Diseases

Cataract – Retinal microvascular abnormalities lead to retinopathy and blindness

Neuropathy
Laboratory Investigations in Diabetes:

- Urine Sugar
- RBS/FBS/PPBS
- GTT
- Glycated Hemoglobin
GALACTOSEMIA

galactitol

galactokinase

galactose 1-phosphate

UDP-glucose

UDP-galactose

lactose  GAG, glycolipids

UDP-glucose

galactose 1-p uridyltransferase

galactose 1-phosphate

glucose 1-phosphate

glucose 6-phosphate

glucose