METABOLISM
Introduction

• The fate of dietary components after digestion and absorption constitute metabolism – regulated by metabolic pathways

• 3 types:
  anabolic pathways- Synthesis of compound – e.g. synthesis protein, triacylglycerol, and glycogen
  Catabolic- breakdown of larger molecules- involve oxidative action, mainly via respiration chain
  Amphibolic pathways – link the anabolic and catabolic pathways
Introduction

• Knowledge of normal mme – important to understand abnormalities underlying disease

• Normal mme – adaptation to periods of starvation, exercise, pregnancy and lactation

• Abnormal mme – result from nutritional deficiency, enzyme def, abnormal secretion of hormones, the action of drugs and toxins – e.g.- diabetes mellitus
Measuring energy changes in biochemistry

Reaction that take places as many part of biochemical processes – hydrolysis of the compound adenosine triphosphate (ATP)
Measuring energy changes in biochemistry

- This reaction release energy - allow energy requiring reaction to proceed
- Adenosine 5’ triphosphate
- Molecular unit of currency of intracellular energy transfer
NAD+, NADH

• Nicotinamide adenine dinucleotide
• Coenzyme found in all living cells
• In mme, involved in redox reactions, carrying electrons from one reaction to another
• NAD+ - an oxidizing agent – accept e and become reduced - forming NADH
• NADH-reducing agent to donate e
Major products of digestion

- Product of digestion – glucose, f.a and glycerol, and aa
- In ruminants-cellulose is fermented by symbiotic microorganisms to short chain f.a (acetic, propionic, and butyric) – mme is adapted to use this f.a as major substrates.
- All products are metabolized to acetyl-COA – then oxidized to citric acid cycle.
Carbohydrate
Simple sugars (mainly glucose)

Protein
Amino acids

Fat
Fatty acids + glycerol

Digestion and absorption

Catabolism

Acetyl-CoA

Citric acid cycle
2H → ATP

2CO₂
DIGESTION AND ABSORPTION OF CARBOHYDRATES
Glycogen, starch, sucrose → Glucose →
- Oxidation via pentose phosphate pathway
- Oxidation via glycolysis
  
Glucose →
- Ribose 5-phosphate
- Pyruvate

Glucose storage
Carbohydrate metabolism

• In aerobic condition- glucose is metabolized to pyruvate through glycolysis and continued to acetyl coa to enter citric acid cycle to complete oxidation to CO2 and H2O- linked to the formation of ATP through oxidative phosphorylation

• Glucose- major fuel of most tissues
Metabolic pathways at different levels of organization

• Amino acid and glucose – absorbed and directed to the liver via hepatic portal vein

• Liver – regulate the blood conc of most water-soluble metabolites

• Excess of glucose is converted to glycogen (glycogenesis) or fat (lipogenesis)

• Between meals, liver maintain blood glucose conc. by glycogenolysis

• Together w kidney – convert non carb metabolites (lactate, glycerol, and aa) to glucose (gluconeogenesis)
Role of liver

- Liver – regulate the blood conc of most water-soluble metabolites
- Excess of glucose is converted to glycogen (glycogenesis) or fat (lipogenesis)
- Between meals, liver maintain blood glucose conc. by glycogenolysis
- Together w kidney – convert non carb metabolites (lactate, glycerol, and aa) to glucose (gluconeogenesis)
- Maintainance of adequate conc of blood glucose- vital- major fuel in brain and the only fuel for erythrocytes
- Synthesize major plasma protein (e.g. albumin) and deaminates excess aa forming urea- to the kidney
Skeletal muscles

- Glucose for fuel – form lactate and CO2
- Stores glycogen as fuel – use in muscular contraction and synthesizes muscle protein fr. Plasma aa
- Muscle~ 50% of body mass- protein storage- can be used to supply aa for gluconeogenesis
Glycolysis & the oxidation of pyruvate

• Glycolysis – principal route for glucose mme and the main pathway for the mme of fructose, galactose, and other carbohydrates derived from the diet.

• Can fx aerobically or anaerobically

• Can provide ATP without O2 – allow muscle perform at very high levels when O2 supply is not sufficient – and allow tissue to survive during anoxic episode
Glycolysis

- Oxidation of glucose or glycogen to pyruvate and lactate
- Similar to the fermentation in yeast cells
End Product of Glycolytic Pathway

- In the presence of O2 - Aerobic

\[
\text{Glucose} + 2\text{NAD}^+ + 2\text{ADP} + 2\text{P}_i \rightarrow 2\text{pyruvate} + 2\text{NADH} + 2\text{H}^+ + 2\text{ATP} + 2\text{H}_2\text{O}
\]

- NADH will enter the electron transfer chain and produce 3 more ATP
- \(2\text{NADH} \rightarrow 6\text{ATP}\)
- Thus total ATP produced : \(8\text{ATP}\)
In anaerobic phase

- Without O2, NADH cannot be reoxidized in e transport chain
- At the same time, cell need NAD+ to continue glycolytic cycle
- Therefore, oxidization of NADH to produce NAD+ occur through conversion of pyruvate to lactate (without producing ATP) by lactate dehydrogenase enzyme
- Therefore, total net ATP produced, 4-2=2 ATP
Regulation of Glycolysis

1) Substrate

**Glucose** – when conc of glc increased, enzymes involved in utilization of glc are activated (glucokinase, phosphofructokinase-1 (PFK) and pyruvate kinase). enz involved for producing glc (gluconeogenesis) are inhibited
2. Hormone
- the secretion of insulin enhances the synthesis of the key enzyme responsible for glycolysis
- Other hormone like epinephrin and glucagon inactivate pyruvate kinase, and thus inhibit glycolysis

3. End products
- PFK are inhibited by citrate and ATP, but activated by AMP
- AMP acts as the energy indicator of energy status of cells
- ATP is used in energy requiring processes – increasing AMP concentration
- Normally conc of ATP is 50 times higher than AMP. Small decrease in ATP, lead to several fold increase conc of AMP. Thus activated PFK to allow more glycolysis to occur
TASK

• LIST CHEMICAL THAT INHIBIT PARTICULAR ENZYME IN GLYCOLYSIS AND THEIR MECHANISM OF INHIBITION
• **Rapoport-Luebering Shunt or Cycle**

• Part of glycolytic pathway in RBC in which 2,3 Biphosphoglycerate is formed as an intermediate between 1,3-BPG and 3-BPG.

Glycolytic pathway in RBC differ with the other tissues...
Role of 2-BPG?

1. Role in Hb
   • In adult Hb- 2,3-BPG will reduce affinity of HB to O2 – excellent O2 carrier
   • In fetal HB – Conc of BPG is low, affinity to O2 is more

2. Role in hypoxia
   • Tissue hypoxia – lead to increase conc of BPG in RBC, thus enhancing unloading of O2 from RB to tissue
Fates of pyruvic acid (PYRUVATE) formed from glucose

1. With O2, oxidatively decarboxylated to **acetylCoA** – ready to enter **kreb cycle** (by pyruvate dehydrogenase)

2. Absence of O2, converted to lactic acid
   - occurs in the skeletal muscle during working conditions
   - pyruvate store H+ from NADH to form NAD+ needed in the glycolysis
   - pyruvate is thus reduced to lactic acid
Anaplerotic reactions

• Sudden influx of acetyl coa- deplete the source of OAA required for the citrate synthase reaction
• Anaplerotic – filling up reactions
• 2 reactions: PA is converted to OAA by pyruvate carboxylase
• Through malic acid formation
Energetics

• 1 molecule of glc produce 2 PA in glycolysis
• By oxidative decarboxilation, 2PA will produce 2 acetyl coa and 2NADH
• 2NADH will be oxidized to 2 molecule of 2NAD+ producing 6 ATP molecules in respiratory chain
Biomedical importance of glycolysis

- Provide energy
- Importance in skeletal muscle - can survive anoxic episode
- Heart muscle - adapted for aerobic condition only, thus has poor survival under ischaemic condition
- Fast growing cancer cells - rate of glycolysis very high, produces more PA than TCA cycle can handle. >>>> of PA lead to >>>> lactic acid production - local acidosis - interfere with the cancer therapy
- Hexokinase deficiency and pyruvate kinase deficiency can cause haemolytic anemia
Utilization of glucose in the body

• After absorption of monosacc into the portal blood, it passes thru the ‘liver filter’ – before ‘presented’ to other tissues for their energy
• In liver:
  Withdrawal of carb from blood
  Release of gluc by liver into the blood
  These processes – finely regulated in the liver cells
  Hepatic cells – freely permeable to glucose
  Other cell – active transport
  Insulin increases uptake of glucose by many extra-hepatic tissues as skeletal muscle, heart muscle, diaphragm, adipose tissue, lactating mammary gland, etc.
Citric acid cycle

- TCA (tricarboxylic acid cycle), krebs cycle
- Final common pathway for breakdown of carb, prot and fats
- Acetylcoa derived from glc, f.a and aa
- Aerobic process, anoxia or hypoxia cause total or partial inhibition of the cycle
- H atoms produced will be transferred to electron transport system to produce ATP molecules
TCA cycle is amphibolic in nature. Why?

TCA has dual role:

• Catabolic – 2 acetyl coa produced are oxidized in this cycle to produce C02, H20, energy as ATP

• Anabolic and synthetic role - Intermediates of TCA cycle are utilized for synthesis of various compounds
Anabolic and synthetic role

1. Synthesis of non essential aa
2. Formation of glucose
3. Fatty acid synthesis
4. Synthesis of cholesterol and steroids
5. Heme synthesis
6. Formation of aceto acetyl coa
TASK

Calculate total ATP produced from glycolysis and TCA cycle per one glucose
Gluconeogenesis

- Glucose is major fuel for some tissues – brain, rbc, testes, renal medulla and embryonic tissues
- Supply of glucose can come from diet, glycogen storage. But glycogen storage are limited – need supply from another sources
- Gluconeogenesis – converts pyruvate and related 3-4C compounds to glucose
- Generally a reverse process of glycolysis
- Mainly in liver, and in renal cortex
Substrate for gluconeogenesis

1. Glucogenic amino acids
2. Lactates and pyruvates
3. Glycerol
4. Propionic acid – important in ruminant
METABOLISM OF GLYCOGEN

- Glycogen – storage of glucose
- Stored in animal body esp in liver and muscles
- Mobilized as glucose whenever the body tissues require
Why store glycogen?

• Insoluble – so will not disturb intracellular fluid content and does not diffuse from its storage site
• Has a higher energy level than glucose
• Readily broken down under influence of enzyme
Glycogenesis

• Formation of glycogen from glucose
• Usually occur in liver and skeletal muscle – can occur in every tissue for some extent
• Liver may contain 4-6% of glycogen per weight of the organ when analysed shortly after a meal high in carbohydrate
• After 12-18 hours of fasting- liver almost depleted of glycogen

• **Glycogen synthase** is the key enzyme
Glycogenolysis

• Breakdown of glycogen to glucose
• Involve phosphorylase enzyme
TASK

• LIST THE GLYCOGEN STORAGE DISEASE IN ANIMALS AND EXPLAIN THE MECHANISMS OF THE DISEASE
17/4/2012
**Glycolysis**

<table>
<thead>
<tr>
<th>Hexokinase</th>
<th>Glucokinase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non specific, can phosphorylate any of the hexoses</td>
<td>Specific, can phosphorylate glucose only</td>
</tr>
<tr>
<td>Found in almost all tissues</td>
<td>Only in liver</td>
</tr>
<tr>
<td>In fetus as well as in adult liver</td>
<td>In adult liver, not in fetus</td>
</tr>
<tr>
<td>Allosteric inhibition by glucose-6-p</td>
<td>Not inhibited by glucose-6-p</td>
</tr>
<tr>
<td>Km is low- high affinity to glucose</td>
<td>Km is high- low affinity to glucose</td>
</tr>
<tr>
<td>Not very much influenced by diabetic state/fasting</td>
<td>Depressed in fasting and diabetes.</td>
</tr>
<tr>
<td>Inhibited by glucocorticoid and GH hormone</td>
<td>Inhibited by glucocorticoid and GH hormone</td>
</tr>
<tr>
<td>Is not effected by insulin</td>
<td>Stimulated by insulin and glucose</td>
</tr>
<tr>
<td>Main fx is to make glucose available to tissues for oxidation at lower blood glucose level</td>
<td>Main fx is to clear glucose from blood after meals and at blood levels greater than 100mg/dl</td>
</tr>
</tbody>
</table>
Glycolysis in animal

- Small animals—can carry oxygen to their muscles fast enough to avoid having to use muscle glycogen anaerobically – migrating birds

- Alligators—when provoked capable of lashing their powerful tails—fast and emergency movements require lactic acid fermentation to provide ATP---- need many hours to clear the excess lactate and regenerate glycogen in muscle

- Other large animals—elephant, rhino, whales – depend on lactic acid fermentation—followed by long recovery periods – exposed to predators

- What about horses?
Dietary polysaccharide and disaccharide

- They are hydrolyzed by enzymes attached to the outer surface of the intestinal epithelial cells.
- The monosaccharide are transported into blood and enter the glycolytic sequence.

\[

dextrin + nH_2O \xrightarrow{\text{dextrinase}} n \text{ D-glucose} \\
\text{Maltose} + H_2O \xrightarrow{\text{maltase}} 2 \text{ D-glucose} \\
\text{Lactose} + H_2O \xrightarrow{\text{lactase}} \text{D-galactose} + \text{D-glucose} \\
\text{Sucrose} + H_2O \xrightarrow{\text{sucrase}} \text{D-fructose} + \text{D-glucose} \\
\text{Trehalose} + H_2O \xrightarrow{\text{trehalase}} 2 \text{ D-glucose}
\]
Lactose intolerance

• Due to the disappearance of lactase activity of the intestinal cells

• Lactose cannot be completely digested and absorbed in the small intestine and passes into the large intestine – bacteria convert it to toxic products that cause abdominal cramps and diarrhea

• Undigested lactose and its metabolites increases the osmolarity of the intestinal contents- cause retention of water in the intestine
Gluconeogenesis

- More than half of glucose requirements are stored as glycogen in muscle and liver
- However this is **not sufficient** – during fasting or vigorous training – glycogen is depleted
- Therefore, gluconeogenesis occur- synthesizing glucose from lactate, pyruvate, glycerol and amino acids
- Majority occur in liver
• TCA cycle intermediates – citrate, isocitrate, α-ketoglutarate, succinyl-CoA, succinate, fumarate and malate – all can undergo oxidation to OAA

• AA that can be metabolized to pyruvate and converted to glucose - glucogenic (e.g -Alanine and glutamine)

• Animals cannot convert acetyl-CoA derived from f.a into glucose, but plants and microorganisms can
Hormones in Gluconeogenesis

- Glucagon - increases gluconeogenesis from lactic acid and amino acids

- Glucocorticoids – stimulate gluconeogenesis by increasing protein catabolism in peripheral tissues and increasing hepatic uptake of amino acids
Pentose Phosphate Pathway

- Also called phosphogluconate pathway and hexose monophosphate pathway
- Oxidation of glucose-6-phosphate to pentose phosphates
- NADP+ is the electron acceptor—yield NADPH
- Pentoses to make DNA, RNA, ATP, NADH, FADH2, and coenzyme A
- NADPH is needed to counter the damaging effects of oxygen radicals
Tissues that carry out extensive f.a synthesis (liver, adipose, lactating mammary gland) or very active synth of cholesterol and steroid hormones (liver, adrenal gland, gonads) required NADPH.

In erythrocytes – NADPH can prevent/undo oxidative damage that is generated by oxygen radicals and prevent genetic defect in Glucose 6-phosphate dehydrogenase.
G6PD

Reductive anabolic pathways

NADPH + H⁺

Glucose 6-phosphate dehydrogenase

Glucose-6-phosphate

6-Phosphogluconate

Ribulose-5-phosphate
- G6PD catalyze the first step, which produces NADPH.
- NADPH protect cells from oxidative damage by hydrogen peroxide (H\textsubscript{2}O\textsubscript{2}) and other superoxide radicals produced as metabolic byproducts and through the action of primaquine (antimalarial drug).
- Normal detoxification: H\textsubscript{2}O\textsubscript{2} is converted to H\textsubscript{2}O by reduced glutathione and glutathione peroxidase.
- Also by catalase.
- **G6PD deficient individuals**—NADPH production is diminished and detoxification is inhibited.
- Lead to **breakdown of erythrocyte** membrane and oxidation of proteins and DNA.
METABOLISM OF GLYCOGEN

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Glycogenesis

1) Glucose-1-Phosphate reacts with Nucleoside triphosphate (UTP), to produce Uridine diphosphate glucose (UDPG)
Glycogenesis

2) Addition of UDPG to glycogenin (glycogen primer) involves formation of a new \( \alpha(1\rightarrow4) \) glycosidic bond. Catalyze by glycogen synthase

3) Synthesis of \( \alpha(1\rightarrow4) \) and \( \alpha(1\rightarrow6) \) glycosidic bond require branching enzyme

The branches grow and further branching
Regulation of glycogenesis

• Controlled by **glycogen synthase (GS)**
• GS ‘a’- active form
• GS ‘b’- inactive
• GS a is converted to GSb through phosphorylation of GS a
• Inactive – glycogenesis is inhibited
• Gsa is converted to GSb through dephosphorylation of serine residue in GSa
• Glycogen breakdown to glucose 1-phosphate

• **Glycogen phosphorylase**-break down the (α-1,4) glycosidic between glucose

• Debranching enzyme -Oligo (α1-6) to (α1-4) glucotransferase transfer the glycogen branches

• Glycogen phosphorylase activity continue
**Glycogenolysis**

- G-1-P released will be converted to G-6-P and can enter glycolysis
- In muscle - G-6-P to support muscle contraction
- In liver – to release glucose into the blood when the glucose level drops – between meals - require glucose-6-phosphatase (in liver and kidney only) to convert to glucose
- Muscle and adipose tissue lack glucose 6-phosphatase, therefore glycogen in these tissues do not contribute to glucose directly to blood
- However G6P can enter glycolytic pathway and forms pyruvate and lactic acid – lactic acid can go to glucose formation in liver
How does an organism ensure glycogen synthesis and breakdown do not occur simultaneously?

- Regulation of glycogen phosphorylase
- Glycogen phosphorylase exist in 2 forms – a (active) and b (less active)
- B predominates in resting muscle
- During vigorous muscular activity epinephrine (in muscle) and glucagon (liver) trigger phosphorylation of a specific Ser residue in phosphorylase B-convert to a
Epinephrin and glucagon will increase the concentration of cAMP that responsible to activates protein kinase A (PKA). PKA phosphorylates and activates phosphorylase b kinase that will catalyzes the phosphorylation of phosphorylase B to A. In muscle, this will provides fuel for ‘fights-or-flight’ action. In liver, provide glucose in blood.
Glycogen storage disease

- Inherited disorders associated with glycogen metabolism
- Deposition of normal or abnormal type and quantity of glycogen in tissues
Regulation of blood glucose

1) Condition of blood glucose in post-absorptive state

- A fasting state – 12 to 14 hours after last meal (no more intestinal absorption)
- Liver glycogen only source of glucose – can supply glucose for additional 8 hours
- Muscle glycogen cannot directly supply glucose to blood due to the lack of glucose-6-phosphatase enzyme
Regulation of blood glucose

2) Condition of blood glucose in postprandial state

• A condition following ingestion of food
• Absorbed monosaccharide are utilized for oxidation to provide energy
• Remaining in excess is stored as glycogen in liver and muscles
• When blood glucose rise beyond renal threshold – glycosurria happen (abnormal)
Auto-regulation

As blood glucose tend to increase
- Increased hepatic Glycogenesis
- Decreased gluconeogenesis
- Decreased output of glucose from liver
- Utilization of glucose by tissues is increase – fall in blood glucose
- Reverse action occurs when glucose blood decrease
- This action depend on the balance between insulin (to lower blood glucose) and glucocorticoid hormone (to increase glucose)
Auto-regulation

As blood glucose tend to decrease
• Decrease in secretion of insulin
• Secretion of glucagon to promote glycogenolysis
• When glycogen supply is not enough, glucocorticoid increase production of blood glucose thru gluconeogenesis
• Decreased glucose utilization
HORMONAL INFLUENCES ON CARBOHYDRATE METABOLISM

1) Insulin
   • Facilitate entrance of glucose into the cells - decreased in blood glucose level

2) Glucagon
   • Increase blood glucose by rapid glycogenolysis in liver
   • Rapid gluconeogenesis from aa, pyruvates and lactates
3) Glucocorticoid

a) Increases blood glucose level thru:
   • Increase protein catabolism in peripheral tissues - so >> amines available for gluconeogenesis
   • Increase hepatic uptake of amines, transaminases
   • Enhancing all important enzymes involved in gluconeogenesis
   • Inhibit glucose uptake in muscles and adipose tissues
   • Stimulate fat breakdown in adipose tissues to provide glycerol as substrate for gluconeogenesis
4) Growth hormone

- Decreases glucose uptake in certain tissues – e.g. muscles

5) Catecholamines – eg epinephrine

- Stimulate glycogenolysis in liver and muscle
- Stimulate ACTH formation, enhancing gluconeogenesis
- Epinephrine inhibited pancreas from release insulin
Blood sugar level and its significance

• Hyperglycaemia – increase in blood glucose level above normal value
• Hypoglycaemia – decrease in blood glucose level below normal value
Hyperglycaemia

Causes:

• Diabetes mellitus – highest values for fasting blood glucose is obtained
• Hyperactivity of thyroids, pituitary and adrenal glands
• Emotional stress
• Pancreatitis and carcinoma of pancreas
etc
Hypoglycaemia

• Over dosage of insulin intake during treatment
• Insulin-secreting tumor of pancreas – abnormal release of insulin
• Hypoactivity of thyroids, hypopituitarism, and hypoadrenalism
• Can be due to the glycogen storage disease – liver phosphorylase deficiency

etc
Glycosuria

• Excretion of glucose in urine which is detectable by Benedicts Qualitative Test

• Due to:
  – Increase in the amount of glucose entering the tubule- above renal threshold level - hyperglycaemic glycosuria
  – Decrease in the glucose reabsorption capacity of the renal tubular epithelium – can be due to kidney disease – renal glycosuria
1) Hyperglycaemic glycosuria

a) Large carbo diet cause blood sugar above renal threshold and glucose utilization is impaired

• These groups should be screened regularly for diabetes

b) Can be due to nervous condition
   – stimulation of nerves to liver and increased secretion of catecholamines—cause glycogenolysis

Students going to exam may have glycosuria
c) Due to endocrine disorders

- DM – B cells of islets linger hands fail to secrete enough amount of insulin – hyperglycaemia
- Increase secretion of epinephrine or prolonged administration – increase glycogenolysis
- Hyperactivity of anterior pituitary
- Hyperactivity of adrenal cortex
- Increased secretion of glucagon by α-cells
Types of Glycosuria

2) Renal glycosuria

a) Hereditary - absence or defective of carrier protein

b) Acquired – damaged in renal tubules – fail to reabsorb glc

heavy metal poisoning – lead, cadmium, mercury – can damage renal tubules

c) Pregnancy may lower the renal threshold
Diabetes Mellitus

1. Primary - due to insufficient insulin
2. Secondary – due to other disease processes

Primary
a) Juvenile onset diabetes – Type 1 – Insulin dependent diabetes mellitus (IDDM)
b) Maturity onset diabetes – Type 2 – Non insulin dependent diabetes mellitus (NIDDM)
Juvenile onset diabetes – Type 1 – Insulin dependent diabetes mellitus (IDDM)

- Results from autoimmune destruction of insulin producing beta cells of the pancreas – lead to decrease in insulin production – increased blood sugars
- Lead to polyuria (frequent urination), polydipsia (increased thirsty), polyphagia (increased hunger)
- Fatal unless treated with insulin
Juvenile onset diabetes – Type 2—Non Insulin dependent diabetes mellitus (NIDDM)

• High blood glucose due to insulin resistance and insulin deficiency
• Obesity is one of the factor
• Insulin resistance – insulin become less effective at lowering blood sugars
• Insulin resistance in liver cells - reduced glycogen synthesis and storage – fail to suppress glucose production
• Insulin resistance in fat cells - reduce normal effects of insulin on lipids, reduced uptakes of circulating lipids and increased mobilization stored lipids
Other factors

- Heredity – both type 1 and 2 are associated with heredity
- Auto immunity in type 1
- Infection – viral infection, eg. Incidence is high after mumps
- Obesity
- Overeating and underactivity
- Insulin resistance
Clinical features and biochemical correlation

- **Glycosuria** lead to osmotic diuresis – lead to large volume of urea (**polyuria**)
- Polyuria lead to thirst (**polydipsia**)
- More fonds of sweet and eats more frequently (**polyphagia**)
- Tissue received glucose but cannot utilize it due to deficiency of insulin (to bring it inside the cell) – cause weakness and tiredness
- Glucose cannot be used - fat is mobilized for energy – lead to increase f.a in blood and liver - lead to increased acetyl CoA – lead to **hypercholestrolaemia** and **atherosclerosis**
Clinical features and biochemical correlation

• Increase acetyl CoA lead to formation of ketone bodies (which is needed to supply energy to brain without glucose),

• but ketone bodies are acidic- excess ketone bodies drop blood pH----ketoacidosis

• lead to fruity smell – due to the presence of acetone

• bicarbonate to buffer the blood pH, thus, lead to hyperventilation to lower the blood CO2 levels
1. Hyperglycaemia - due to impaired transport and intake of glucose in muscles
   - repress key glycolytic enzyme
   - derepress key gluconeogenic enzyme – promoting gluconeogenesis in liver – further contribute hyperglycaemia

2. Transport and uptake of aa in peripheral tissue is also depressed
   – elevated circulating level of aa esp alanine - fuel for gluconeogenesis in liver. Aa breakdowns lead to increased production of urea N

3. Protein synthesis is decreased

4. Synthesis of fa and TG decrease due to decreased of acetyl CoA

5. Lipid storage are hydrolysed produce free f.a to produce energy
   – stimulate gluconeogenesis --- hyperglycaemia
Metabolic changes in DM

7. Acetyl CoA can no longer enter TCA cycle (due to decrease in OAA which is due to no glucose) – is channeled to cholesterol synthesis and ketone bodies formation

8. Glycogen synthesis is depressed due to decreased glycogen synthase activity due to deficiency of insulin

9. Glycosylation of Hb lead to Glycosylated of Hb (HbA1c) – Hb A1c is used for diabetic monitoring

10. Glycosylation of other proteins as plasma albumin, collagenous tissues and α- crystallin (protein of lens and cornea) – caused thickening of the cells and morphological changes of vessel walls

11. Cataract in lens – due to the glycosylation of α- crystallin and accumulation of sorbitol which produces osmotic damages
Complications of DM

- **IMMEDIATE**- Ketoacidosis lead to coma
- **LATE COMPLICATIONS** – Due to the changes in blood vessels – large and small vessels
  - Large – atherosclerosis – myocardial infaction, stroke
  - Small – thickening of basement membrane, microvascular changes
    - Diabetic retinopathy – blindness
    - Diabetic cataract
    - Diabetic nephropathy
    - Neuropathy – loss of sensation and tingling – due to myoinositol deficiency
    - Gangrene – diminished blood supply due to atherosclerosis – also associated with tissue hypoxia due to formation of HbA1c – less O2 carrying capacity
<table>
<thead>
<tr>
<th>IDDM</th>
<th>NIDDM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less common</td>
<td>More common</td>
</tr>
<tr>
<td>In young individual</td>
<td>In older individual</td>
</tr>
<tr>
<td>Onset – rapid and abrupt</td>
<td>Onset - insidious</td>
</tr>
<tr>
<td>Speedy progression to ketoacidosis and coma</td>
<td>Usually mild – ketoacidosis is rare</td>
</tr>
<tr>
<td>Patients are thin and underweight</td>
<td>obesity</td>
</tr>
<tr>
<td>At first-juvenile diabetics produce more insulin than normal. Patients become overt diabetics with atrophied B cells and no insulin</td>
<td>B cells respond normally, but deficiency is due to the Insulin antagonism</td>
</tr>
<tr>
<td>Plasma insulin almost absent- no insulin response to glucose load</td>
<td>Insulin antagonism</td>
</tr>
<tr>
<td>Insulin therapy is necessary</td>
<td>Oral hypoglycaemic and dietary control</td>
</tr>
</tbody>
</table>
READING

• BACTERIAL DNA EXTRACTION USING QIAGEN KIT

• POLYMERASE CHAIN REACTION

• GEL ELECTROPHORESIS