Diabetes Mellitus (DM)

Dr Jemil Makadia

Introduction

- Its group of metabolic disorders characterized by hyperglycemia due to insulin deficiency or decreased glucose utilization
- **Types**
  - Type-I DM (IDDM)
  - Type-II DM (NIDDM)
  - MODY (Maturity Onset Diabetes of Young)
  - Gestational diabetes

- **Type-I DM (IDDM)**
  - Due to pancreatic beta cell destruction
  - Insulin deficiency
  - More common in children & adults < 30 years
  - Insulin dependent
  - Prone to develop ketosis
  - IA- due to autoimmune reaction to B-cell
  - IB- idiopathic
- **Type-II DM (NIDDM)**
  - Insulin resistance, impaired insulin secretion and increased glucose production
  - More common with increasing age

- **MODY (Maturity Onset Diabetes of Young)**
  - Early onset of hyperglycemia and impaired secretion of insulin
  - Autosomal dominant
  - Types- MODY 1-6
  - Insulin resistance
  - Present like type-II DM
- **Gestational diabetes**
  - Insulin resistance seen in late pregnancy
  - Leads to impaired glucose tolerance and even frank diabetes
  - Normal glucose tolerance after delivery
  - Increased risk of developing DM in future

Metabolic changes

- Insulin resistance present in tissue which unable glucose utilization
- DM resemble starvation
- GLUT-4 depends on insulin- present in skeletal muscle and adipose tissue

(1) Hyperglycemia

  - Increase gluconeogenesis
  - Underutilization of glucose

(2) Lipolysis

- Long standing DM
- Due to low Insulin : Glucose ratio

- Activate hormone sensitive lipase

- Lipolysis

- Increase FFA and glycerol
- Excess FFA taken up by tissue for B-oxidation
- High ATP, NADH and low oxaloacetate inhibit glycolysis and TCA

(3) Ketosis & Hyperlipidemia

- Acetyl CoA from B-oxidation diverted to ketosis, cholesterol synthesis and fatty acid synthesis in liver
- Increase ketone bodies formation by liver leads to keto acidosis
- Influx of acetyl CoA and FFA in liver produces TG, which is excreted from liver into VLDL and then into LDL
- Decrease lipoprotein lipase activity in DM leads to decrease chylomicron and VLDL metabolism

- Leads to hypertriglyceridemia and hypercholesterolemia

(4) Protein catabolism and muscle wasting

- Low insulin levels decrease protein synthesis
- Increase urea synthesis
- Muscle wasting will occur

(5) Long standing metabolic effects

- Mainly affected tissues are
  - RBC, Brain, Intestine, Kidney, Peripheral nerve, Retina and Eye lens
- Aldose reductase(Polyol pathway)
  - High Km
  - Activated in DM
  - Cataract formation

Advanced Glycation End products (AGEs)

- **Glycation**- Refers to non-enzymatic attachment of sugars (glucose) to amino groups of protein (Hb, Albumin, Collagen and cellular matrix proteins) and also to the other molecules (DNA, Lipids)
- **Glycosylation**- Enzyme catalyzed attachment of sugars

- Hb-NH2 + Glucose

- Glycated-Hb (Schiff base)

Amodori rearrangement

- HbA1c (ketoamine)

- Further rearrangements to AGEs

- This reactions known as MILLARD REACTION
- Browning of food stuffs on storage and heating

- Aging
- Atherosclerosis
- AGE receptor on macrophages and endothelial cells

- Taken up glycated proteins

- Activate transcription factor NFkB

- Release of cytokines and pro inflammatory molecules

Clinical Features

- **Polyurea**
  - Increase in urine output and frequency
  - Increase glucose leads to increase glucose in urine, which require large amount of water for excretion
- **Polydipsia**
  - Polyurea leads to dehydration
  - Increase thirst and polydipsia
- **Polyphagia**
  - Due to insulin deficiency and resistance, cell are starving as glucose can’t enter the cell
  - So increase in hunger

Diagnosis

mg/dl	Normal	IGT	DM
Fasting	70-110	110-126	>126
PP2BS	<140	140-200	>200
Random	<200	-	-

- Hb
  - HbA1 (97%)
    - HbA1a, HbA1b, HbA1c (Attached to glucose)
  - HbA2 (2.5%)
  - HbF (0.5%)
- Glycation is irreversible process
- Give average blood glucose level as binding to Hb remain thrughout lifespan of RBC (120 days)
- Normal- 4-6%
- DM- > 6.5%
- Target for control- <7%

Metabolic syndrome

Also known as Syndrome X and Insulin resistance syndrome

- Insulin resistance
- Hypertension
- Dyslipidemia
- Central obesity
- Atherosclerosis

Complication

- **Acute**
  - Diabetic ketoacidosis (DKA)
  - Hyperglycemic non ketotic hyperosmolar state
- **Chronic**
  - **Microvascular**
    - Retinopathy & macular edema- blindness
    - Neuropathy
    - Nephropathy

- **Macrovascular**
  - CAD & MI
  - Cerebrovascular d's (Stroke)
  - Peripheral vascular disease
- **Other**
  - Cataract & glaucoma
  - Infections

- **DKA**
  - DM-I, Emergency
  - Severe hyperglycemia
  - Ketosis (increase KB- Acetone), Acidosis
  - Hyperventilation (fruity odor)
  - Nausea, vomiting, pain abdomen, lethargy, depression, drowsy
  - Acidosis with anion gap
  - Hyperkalemia, Hyponatremia
  - Treatment
    - IV Insulin
    - Fluids
    - electrolytes

- **Non-ketotic hyperosmolar coma**
  - DM-II
  - Due to insulin insufficiency with inadequate fluid intake
  - No ketosis
  - Hyperglycemia (>500 mg%)
  - Electrolytes are normal
  - Acidosis not significant
  - Normal anion gap
  - Plasma osmolality increases

Thank you