Diabetes Mellitus

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Surat
What is diabetes?

- Group of diseases
- High levels of blood glucose
- Due to defects in insulin production
- Due to defects in insulin action
- Both.

- Metabolic disorder
- Chronic hyperglycaemia
- Disturbances of carbohydrate, fat and protein metabolism
Diabetes – Clinical Features

Common Representation
- Polyuria
- Polyphagia
- Polyuria
- Weight loss.
- Blurring of vision

Severe forms
- Ketoacidosis
- Non–ketotic hyperosmolar state
Later Symptoms

- Fatigue
- Dry skin
- Recurrent infection
- Feet Ulceration
- Sensory loss in lower extremities
- Erectile dysfunction
- Slow Healing of wounds
- Visual disturbance
Types of Diabetes

- Type 1 Diabetes Mellitus
- Type 2 Diabetes Mellitus
- Gestational Diabetes
- Other types:
  - LADA (Latent Autoimmune Diabetes of Adult Onset)
  - MODY (Maturity Onset Diabetes of Young)
    - Mutation in Gene
  - Secondary Diabetes Mellitus
Type 1 diabetes

- Insulin-dependent diabetes mellitus (IDDM)
- Juvenile-onset diabetes.
- Immune system destroys pancreatic beta cells
- Children and young adults
- Although disease onset can occur at any age.
- Type 1 diabetes may account for 5% to 10% of all diagnosed cases of diabetes.
Type 2 diabetes

- Non-insulin-dependent diabetes mellitus (NIDDM)
- Adult-onset diabetes.
- 90% to 95% of all diagnosed cases of diabetes.
- Insulin resistance
- As the need for insulin rises
- & Pancreas gradually loses its ability to produce insulin.
- Associated with
  - Older age
  - Obesity & Physical inactivity
  - Family history of diabetes & History of gestational diabetes
  - Impaired glucose metabolism
Type 1 Diabetes: Insufficient Insulin

- Diminished insulin
- Glucose

Type 2 Diabetes: Insulin Resistance

- Insulin
- Glucose

Fat/muscle cells

- Insulin receptors
- Glut-4
- Glucose transporters
- Diminished glucose uptake

Defect in signaling to Glut-4
- Glucose transporters
- Diminished glucose uptake
Gestational diabetes

- Diagnosed in some women during pregnancy.
- After pregnancy, 5% to 10% of women with gestational diabetes are found to have type 2 diabetes.
Other types of DM

- **Maturity Onset Diabetes of Young**
  - Surgery
  - Drugs
  - Malnutrition
  - Infections
  - Other illnesses.

- 1% to 5% of all diagnosed cases of diabetes.
LADA

- Latent Autoimmune Diabetes in Adults (LADA)
- *Autoimmune type 1 diabetes* at older age
- "Slow Onset Type 1" diabetes
MODY

- MODY – Maturity Onset Diabetes of the Young
- Mutations
  - In enzyme glucokinase
  - In Receptor
- In sufficient insulin release from pancreatic β-cells
Secondary DM

Secondary causes of Diabetes mellitus include:

- Acromegaly
- Cushing syndrome
- Thyrotoxicosis
- Pheochromocytoma
- Chronic pancreatitis
- Cancer
- Drug induced hyperglycemia
## Reference Ranges

<table>
<thead>
<tr>
<th></th>
<th>FBS in mg%</th>
<th>PP2BS in mg%</th>
<th>HbA1C in %</th>
</tr>
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<tbody>
<tr>
<td><strong>Normal</strong></td>
<td>70 – 110</td>
<td>&lt; 140</td>
<td>4 – 6.5</td>
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<tr>
<td><strong>Pre-Diabetic</strong></td>
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Investigation

- FBS
- PP2BS
- Oral Glucose Tolerance Test
- I.V. Glucose Tolerance Test
- HbA1C
- Urinary Sugar - Protein
- Lipid Profile
- Renal Function Test
- Fundus Examination
- Nerve Conduction Study
Complications

- Acute complications
- Chronic complications
Acute complications

- Diabetic Ketoacidosis
- Hyperosmolar Non-ketosis Coma
- Hypoglycemia
Diabetic ketoacidosis (DKA)

- Acute and dangerous
- On presentation at hospital,
  - Dehydrated
  - Hypotension & shock.
  - Breathing = Rapid and Deep.
  - Kussmull’s breathing
  - Fruity smell from breath
  - May progress to coma.
Investigation in DKA

- Electrolyte
- Blood Glucose
- Blood Ketone body
- ABG
  - pH
  - pO2
  - pCO2
  - HCO3-
Hyperosmolar Nonketotic Coma

- Symptoms are similar to DKA
- Due to osmotic effect of high glucose levels
- Water loss increases and eventually lead to dehydration.
- Progressively dehydrated
- Electrolyte imbalance.
- Lethargy
- Ultimately progress to a coma
Hypoglycemia

- Due to several diabetes treatments.
- Sweaty & Weak.
- Altered Consciousness
- Coma, Seizures
- **Caused by**
  - Too much dose of insulin or oral hypoglycemic drugs.
  - Incorrectly timed insulin
  - Too much or incorrectly timed exercise
  - Not enough food
Chronic complications

- Microvascular diseases
- Macrovascular diseases
  - Coronary artery disease
  - Peripheral vascular disease
  - Intermittent claudication
  - Stroke
  - Diabetic foot
- Most Common Pathogenesis for Chronic complication in DM, is AGE
Microvascular diseases

- Diabetic cardiomyopathy,
- Diabetic nephropathy
- Diabetic neuropathy
- Diabetic retinopathy
Advance Glycate End-Products

- It is “Non-Enzymatic Glycation of Protein or Lipid”
  - Protein /Lipid attached with Glucose, without Enzyme
  - This is called “Glycation” or “AGEs”
- Because of Protein Glycation
  - Protein structure get change
  - Protein denaturation
  - Protein function get affected because of protein glycation
Advance Glycate End-Products in Diabetes Mellitus

- Artery – Vessels – capillary
  - Arteriosclerosis, Atherosclerosis
- Eye lens
  - Cataract
- Glomerulus membrane
  - Nephropathy
  - CRF
- Nerves – Motor nerve, Sensory Nerve, Optic nerve
  - Motor & Sensory Neuropathy
  - Optic neuropathy
- Plasma protein – Haemoglobin, Albumin
  - HbA1C
Advance Glycate End-Products

- Glycate Haemoglobin – HbA1c
  - Life of HbA1c = 3 – 4 months = Life of RBC
  - Significant
    - Prognosis of DM patient
    - Chance of complication of DM
    - Glycation control of last 3 months
Management of Diabetes Mellitus
The major components of the treatment of diabetes are:

- **A** • Diet and Exercise
- **B** • Oral hypoglycaemic therapy
- **C** • Insulin Therapy
Diet & Exercise

- **Dietary treatment should aim at:**
  - Ensuring weight control
  - Providing nutritional requirements
  - Allowing good glycemic control
  - Correcting any associated blood lipid abnormalities

- **Exercise**
  - Reduce abdominal obesity
  - Minimum 30 – 40 minutes brisk walking
  - Aerobic exercise
**Nutritional Requirement**

- **Carbohydrate**
  - 60-70% calories from carbohydrates & monounsaturated fats
- **Protein**
  - 10-20% total calories
- **Fat**
  - <10% calories from saturated fat
  - 10% calories from PUFA
  - <300 mg cholesterol
- **Fiber**
  - 20-35 grams/day
- **Alcohol**
  - Type I – limit to 2 drinks/day, with meals
  - Type II – substitute for fat calories
B. Oral Anti-Diabetic Agents

- Classes of Oral anti-diabetic agents:
  1. Sulfonylureas
  2. Biguanides
  3. Thiazolidinediones
  4. Alpha-glycosidase inhibitors
  5. Meglitinides
  6. Dipeptidyl peptidase-4 inhibitor
Sulfonylureas

Mechanism : Stimulation of insulin secretion

1st generation:
  Tolbutamide
  Chlorpropamide

2nd generation:
  Glybenclamide
  Glipizide

3rd generation:
  Glymepiride
Biguanides

- Phenformin
- Metformin

- **Mechanism**
  - Decrease glucose production from Liver by mild inhibiting ETC complex –I
  - Decrease intestinal absorption of Glucose
Thiazolidinediones (TZDs)

- Representative Drugs
  - Rosiglitazone
  - Pioglitazone
- Pharmacological effects
  - Improving function of insulin sensitivity
  - Decrease insulin resistance
α-glucosidase inhibitors

- **Representative Drugs**
  - Acarbose
  - Voglibose

- **Mechanism**
  - Competitively inhibiting alpha amylase
  - To inhibit digestion of starch & disaccharides

- Main adverse reaction
  - Flatulence, diarrhea.
Meglitinides

- **Representative Drugs**
  - Repaglinide

- **Key point**
  - Increase insulin release by inhibiting ATP-sensitive K$^+$-channel
  - No direct effect on insulin release
  - Used alone or together with biguanides
  - Carefully used for patients with kidney or liver impaired.
Dipeptidyl Peptidase-4 (DPP) Inhibitor

- Sitagliptin
- Saxaliptin

**Mechanism of Action**
- DPP-4 inactivate Incretins
- So DPP-4 inhibitor increase incretins
- Inhibit insulin degradation
- Decrease Glucagon
Indication of Insulin Therapy

Short-term use:
- Acute illness, surgery, stress and emergencies
- Pregnancy
- Insulin may be used as initial therapy in type 2 diabetes
- in marked hyperglycaemia
- Diabetic ketoacidosis
- Hyperosmolar nonketotic coma

Long-term use:
- If targets have not been reached after optimal dose of combination therapy
<table>
<thead>
<tr>
<th>Types of insulin</th>
<th>Brand names</th>
<th>Basal/bolus</th>
<th>Dosing schedule</th>
</tr>
</thead>
</table>
| **Rapid-acting analogue**| Humalog® (insulin lispro)  
NovoRapid® (insulin aspart) | Bolus       | Usually taken right before eating or to lower high blood glucose |
| (clear)                  |                      |             |                                                      |
| Onset: 10–15 minutes     |                      |             |                                                      |
| Peak: 60–90 minutes      |                      |             |                                                      |
| Duration: 4–5 hours      |                      |             |                                                      |
| **Short-acting**         | Humulin®-R           
Novolin®ge Toronto | Bolus       | Taken about 30 minutes before eating, or to lower high blood glucose |
| (clear)                  |                      |             |                                                      |
| Onset: 0.5–1 hour        |                      |             |                                                      |
| Peak: 2–4 hours          |                      |             |                                                      |
| Duration: 5–8 hours      |                      |             |                                                      |
| **Intermediate-acting**  | Humulin®-N           
Novolin®ge NPH | Basal       | Often taken at bedtime, or twice a day (morning and bedtime) |
| (cloudy)                 |                      |             |                                                      |
| Onset: 1–3 hours         |                      |             |                                                      |
| Peak: 5–8 hours          |                      |             |                                                      |
| Duration: up to 18 hours |                      |             |                                                      |
| **Extended long-acting** | Lantus® (insulin glargine)  
Levemir® (insulin detemir) | Basal       | Usually taken once or twice a day                   |
| analogue** (Clear and colourless) |                    |             |                                                      |
| Onset: 90 minutes        |                      |             |                                                      |
| Peak: none               |                      |             |                                                      |
| Duration: 24 hours       |                      |             |                                                      |
| **Premixed**             | Humalog® Mix 25™  
Humulin® (20/80, 30/70)  
Novolin®ge (10/90, 20/80, 30/70, 40/60, 50/50) | Combination of basal and bolus insulins | Depends on the combination |
| (cloudy)                 |                      |             |                                                      |
| A single vial contains a fixed ratio of insulins (the numbers refer to the ratio of rapid- or fast-acting to intermediate-acting insulin in the vial) | | | |
Treatment of DKA

1. Improve circulatory volume
2. Decrease Serum glucose
3. Clear serum of ketonebodys
4. Correct electrolyte imbalances
Treatment of DKA

Principles of Treatment:

• Replacement of fluid deficits.
• Correction of acidosis & hyperglycemia via Insulin administration.
• Correction of electrolytes imbalance.
• Treatment of underlying cause.
Fluids replacement

Intravenous solutions
- Replace extravascular and intravascular fluids
- Replace electrolyte losses
- Dilute both the glucose level

Insulin is needed to help
- switch from a catabolic state to an anabolic state
- uptake of glucose in tissues
- reduction of gluconeogenesis
- reduce ketone production.
Fluid Correction

- Initial correction of fluid loss is either
  - by isotonic NaCl solution
  - by lactated Ringer solution.
- The recommended schedule:
  - Administer 1 - 3 L during the first hour.
  - Administer 1 L during the second hour.
  - Administer 1 L during the following 2 hours
  - Administer 1 L every 4 hours
- When blood sugar < 180 mg/dL
  - 5-10% dextrose with half isotonic NaCl solution.
- In maintainance, half-normal saline at 200-1000 mL/h
Insulin Therapy

- Regular insulin infusion = 0.1 U/kg/hour
- Serum Glucose should not decrease more than 100mg%/hour
- If Glucose falls < 200 prior to correction of acidosis,
  - change IV fluid from 5% Dextrose or 10% dextrose
  - But don’t decrease the rate of insulin infusion.
- Use initial bolus of insulin (IV/IM) is controversial.
Correction of Acidosis

- Insulin therapy
  - Stops Lipolysis
  - Decrease production of ketone bodies.
- Normal saline
  - Correction of dehydration
  - Normalize the blood PH.
- Bicarbonate therapy
  - should not be used unless severe acidosis (pH<7.0)
Correction of Electrolyte Imbalance

- If K+ is low.
  - As soon as the urine output is restored, potassium supplementation
- If K+ is high
  - Potassium should be corrected
    - Furosemide
    - Insulin
    - Salbutamol
    - Bicarbonate
Thank You