Diabetes Mellitus

• Disorder of metabolism (Carb, Prot & Fat)
• Due to Absolute/relative deficiency of insulin.
• Characterized by hyperglycemia.

• Clinically: Polyuria, Polydypsia, Polyphagia.
Diabetes Classification

- Type 1A: Immune Mediated
  Type 1B: Insulin deficient, no autoantibodies
- Type 2: No Autoantibodies, Can initially be treated without insulin
- Other Specific forms of Diabetes
- Gestational Diabetes
Classification

- **Primary DM** – (primary - no other disease)
  - Type I – IDDM / Juvenile – 10%.
  - Type II – NIDDM / Adult onset – 80%.
  - MODY – 5% maturity onset - Genetic
  - Gestational Diabetes

- **Secondary DM** – (secondary to other dis.)
  - Pancreatitis/tumors/Hemochromatosis.
  - Infectious – congenital rubella, CMV.
  - Endocrinopathy, downs.
  - Drugs – Corticosteroids.
Introduction

• Diabetes mellitus (sweet urine)
• 3% of world population, 100 million people
• Incidence is increasing alarmingly (40% in the past decade, more in future. 259 m by 2025.
• Most Common non communicable disease
• High Morbidity & mortality.
• DM shortens life span by 15 years.
• Leading cause of blindness and Kidney dis.
• Pacific Islands – leaders in DM & Obesity…!
Insulin Actions

- Transmembrane transport of glucose
- Liver, muscle & fat $\rightarrow$ ↓ blood glucose
- Liver & skeletal muscle - ↑ glycogen
- Converts glucose to triglycerides
- Nucleic acid & Protein synthesis
- Diabetes $\rightarrow$ Increased catabolism.
- Hyperglycemia, ↓ protein synthesis, Liplysis, wasting, weight loss.
Blood Glucose & Hormones

Hormone
- Insulin
- Glucocorticoids
- Glucagon
- Growth Hormone
- Epinephrine

Action
- ↓ Glucose
- ↑ Glucose
- ↑ Glucose
- ↑ Glucose
Cellular Glucose Uptake

**Insulin Requiring**
- Striated Muscle
- Cardiac Muscle
- Fibroblasts
- FAT

**Non-Insulin Requiring**
- Blood Vessels
- Nerves
- Kidney
- Eye Lens
Pathology in Diabetes:

- **Low glucose inside cell**
  - decreased cell metabolism (muscle, liver)
- **High glucose outside**
  - Glycosylation damage (BV)
  - Polyol products – osmotic damage*
Pathogenesis of Type I DM

Genetic
HLA-DR3/4

Environment
Viral infection?

Autoimmune Insulitis
Ab to β cells/insulin

β cell
Destruction

Type I / IDDM

Insulin deficiency

- PS Glomerulonephritis
- Graves, Hashimoto thyroiditis.
- Rheumatic heart disease
- SLE, Collagen vascular disease
- Rheumatoid arthritis.
“Stages” in Development of Type 1A Diabetes

- Genetic Predisposition
- (?Precipitating Event)
- Overt immunologic abnormalities
- Progressive loss insulin release
- Normal insulin release
- Glucose normal
- Overt diabetes
- C-peptide present
- No C-peptide
Pathogenesis of Type II DM

- Genetic / β cell defect
- Obesity / Life style?
- Abnor. Secretion
  - Insulin Resistance
  - Relative
  - Insulin Def.

Type II NIDDM
<table>
<thead>
<tr>
<th>Type-I</th>
<th>Type-II</th>
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</thead>
<tbody>
<tr>
<td>• Less common</td>
<td>• More common</td>
</tr>
<tr>
<td>• Children &lt; 25 Years</td>
<td>• Adult &gt;25 Years</td>
</tr>
<tr>
<td>• Insulin-Dependent</td>
<td>• Insulin Independent *</td>
</tr>
<tr>
<td>• Duration: Weeks</td>
<td>• Months to years</td>
</tr>
<tr>
<td>• Acute Metabolic complications</td>
<td>• Chronic Vascular complications.</td>
</tr>
<tr>
<td>• Autoantibody: Yes</td>
<td>• No</td>
</tr>
<tr>
<td>• Family History: No</td>
<td>• Yes</td>
</tr>
<tr>
<td>• Insulin levels: very low</td>
<td>• Normal or high *</td>
</tr>
<tr>
<td>• Islets: Insulitis</td>
<td>• Normal / Exhaustion</td>
</tr>
<tr>
<td>• 50% in twins</td>
<td>• 60-80% in twins</td>
</tr>
</tbody>
</table>
Complications:

• Short term Complications: (metabolic)
  – Hypoglycemia
  – Diabetic Ketoacidosis
  – Non Ketotic hyperosmolar diabetic coma
  – Lactic acidosis

• Long term Complications: (Angiopathy)
  – Micronangiopathy - Retinopathy, Nephropathy, Neurophathy, dermatopathy.
  – Macroangiopathy – Atherosclerosis.
Microangiopathy Pathogenesis:

- Hyperglycemia chronic.
- Excess deposition of proteins – glycosylation cycle.
- Thick and Leaky blood vessels.
- Narrow lumen
- Ischemic Organ damage...
Diabetic Microangiopathy

- Glucose
- Glycosylation
- BM damage leak
- ‘AGE’ deposition
Nephropathy

- Nodular Glomerulo Sclerosis.
- Common morbidity & mortality.
- Deposition of ‘AGE’ Advanced Glycosylation End-products as nodules.
- Nephrotic syndrome
- Pyelonephritis
- End stage renal failure
Diabetic Nephropathy

Microangiopathy, atherosclerosis & infections:

- Diffuse or nodular diabetic glomerulosclerosis (Kimmelstiel Wilson Sy)
- Renal arteriolosclerosis & atherosclerosis
- Necrotizing renal papillitis.
- Pyelonephritis.
- End stage kidney.
Nodular Glomerulosclerosis – KW lesion.
Normal Retina
Non Proliferative Retinopathy

- Venous dilation and small **red dots** posterior retinal pole - capillary micro-aneurysms.
- **Dot and blot** retinal hemorrhages and deep-lying edema and lipid exudates impair macular function.
- Late generalized diminution of vision due to **ischemia** and **macular edema** - common cause of visual defect (best detected by fluorescein angiography)
- **Cotton-wool spots** (soft exudates) - microinfarcts due to ischemia. They are white and obscure underlying vessels. Hard exudates are caused by chronic edema. They are yellow and generally deep to retinal vessels.
Proliferative Retinopathy

- Neovascularization - which grows into the vitreous cavity.
- In advanced disease, neovascular membranes can occur, resulting in a traction retinal detachment.
- Vitreous hemorrhages may result.
- Sudden severe loss of vision can occur when there is intravitreal hemorrhage.
- Poor visual prognosis if severe retinal ischemia, extensive neovascularization, or extensive fibrous tissue formation.
- Panretinal photocoagulation may diminish or eliminate proliferative retinopathy
Diabetic Retinopathy
Pre retinal Hemorrhage - detachment
Diabetic Retinopathy
Advanced fibrous plaques
Macroangiopathy Atherosclerosis

- Dyslipidemia
- ↓ HDL
- Non-Enzymatic Glycosylation
- ↑ Platelet Adhesiveness
- ↑ Thromboxane A₂
- ↓ Prostacyclin
- **Endothelial damage** → Atherosclerosis
- MI, CVA, Gangrene of Leg (PVD), Renal Insufficiency
Infections in Diabetes:

• Decreased metabolism – low immunity.
• Decreased function of lymphocytes & neutrophils – glycosylation.
• Glycosylation of immune mediators. Ab
• Capillary thickening – impaired inflammation.
• Ischemia & infarctions.
• Increased glucose (alone is not the cause*)

• Diabetes → State of immunosuppression.
Laboratory Diagnosis:

- Urine glucose - dip-stick – Screening
- Random or fasting blood glucose (<11)
- Fasting > 7mmol, Random >11mmol
- If Fasting level is between 7-11 then OGTT

- HbA1c - for follow-up, not for diagnosis
- Fructosamine - for long term maintenance.
Points to remember:

• Disorder of metabolism – Insulin
• Type-I Children, Acute, Metabolic compl.
• Type-II Adults, Chronic, Vascular compl.
  – Angiopathy (micro/macro),
  – Heart, Brain, Kidney, Retina, Skin, BV.
• Increased Infections – know reasons.
• Hypoglycemia is more dangerous. Not hyper
• Glucose control is critical *
• FBS, GTT & HbA1C.