### Management of Diabetes Mellitus

#### Specific Goals in Management of Diabetes
- Fasting < 100 mg/dL
- Post-meal < 140 mg/dL
- A1C < 7%
- Blood Pressure < 130/80
- LDL < 100 mg/dL; HDL > 45 mg/dL
- Triglycerides < 150 mg/dL

#### Treatment of Diabetes Mellitus
1. Education
2. Diet
3. Physical exercise
4. Oral antidiabetic drugs
5. Insulin
6. Islet cell transplantation

#### Pancreatic Islet Function Determines Onset of IGT and T2DM in an Insulin-Resistant Setting

#### Non-pharmacological management of T2DM (lifestyle intervention)
1. Diet
   - a. Decrease fat content and total calories
   - b. Decrease saturated fat
   - c. Decrease salt for hypertension
   - d. Individualized diet
   - e. Weight reduction in obese patients
2. Exercise
   - a. Increase energy expenditure with moderate-intensity exercise
   - b. Reduce cardiovascular risk factors
3. Smoking cessation

#### Education
1. Nature & emergencies of the Ds
2. Diet, drug therapy
3. Follow up

#### Exercise → Regular exercise promote better glucose uptake by cells

#### Oral Antidiabetics
1. Sulfonylureas
2. Thiazolidinediones
3. Biguanides
4. Alpha-glucosidase inhibitors
5. D-phenylalanine derivatives
6. Incretin based therapies (DPP-4 i)

### Pharmacologic Targets of Current Drugs Used in the Treatment of T2DM

<table>
<thead>
<tr>
<th>GLP-1 analogs</th>
<th>Improve pancreatic islet glucose sensing, slow gastric emptying, improve satiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Increase glucose uptake and decreases hepatic glucose production</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>Increase insulin secretion from pancreatic β-cells</td>
</tr>
<tr>
<td>Glinides</td>
<td>Increase insulin secretion from pancreatic β-cells</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>Delay intestinal carbohydrate absorption</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>Decrease lipolysis in adipose tissue, increase glucose uptake in skeletal muscle and decrease glucose production in liver</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Prolong GLP-1 action leading to improved pancreatic islet glucose sensing, increase glucose uptake</td>
</tr>
</tbody>
</table>
### Sulphonylureas

**Actions**
1. Promote release of insulin from \( \beta \)-cells through
2. ↓ hepatic glucose production
3. Insulin sensitizing effect

**Classification**

<table>
<thead>
<tr>
<th>Pharmacological</th>
<th>Trade name</th>
<th>Duration of action</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide</td>
<td>Rastinon</td>
<td>short acting (6h)</td>
<td>0.5-2 gm</td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>Dimelor</td>
<td>intermediate (12h)</td>
<td>0.25-1.5 gm</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>Paiddine</td>
<td>long acting (24h)</td>
<td>0.05 gm</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Minidiab</td>
<td></td>
<td>2.5-30 mg</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>Diamicon</td>
<td>6</td>
<td>12-24 mg</td>
</tr>
<tr>
<td>Gliclazide MR</td>
<td>Diamicon MR</td>
<td>24</td>
<td>-120 mg</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>Daonil</td>
<td>12-24</td>
<td>2.5-15 mg</td>
</tr>
<tr>
<td>Glimpride</td>
<td>Amaryl</td>
<td>24</td>
<td>1-8 mg</td>
</tr>
</tbody>
</table>

**How it works**
Simulation of insulin secretion from pancreatic B cell
Decrease hepatic glucose release

**Attributes**

<table>
<thead>
<tr>
<th>How it works</th>
<th>Efficacy</th>
<th>Adverse effect</th>
<th>Advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Hypoglycemia</td>
<td>Extensive experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Wight gain</td>
<td>↓ Microvascular risk (related to glucose control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B Cell Exhaustio</td>
<td>Low cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chloretic jaundice</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypersensitivity reactions</td>
<td></td>
</tr>
</tbody>
</table>

**Drug reaction with sulphonylurea**

- Anticoagulants
- Salicylates
- Sulphonamides
- MAO Inhibitors
- Tricyclic antidepressants
- Azole antifungals

**Indication**
- Used alone in obese type 2 DM not controlled by diet alone
- Combined with sulphonylurea or insulin to achieve control

### Biguanides - euglycemic (insulin sensitizers)

**Action**
1. ↓ hepatic glucose production
2. ↑ anaerobic glycolysis (T lactic acid formation from glucose)
3. ↑ sensitivity of insulin receptor
4. ↓ appetite & glucose absorption from the gut
5. Beneficial effect on lipid profile

**Indication**
- Used alone in obese type 2 DM not controlled by diet alone
- Combined with sulphonylurea or insulin to achieve control

**Preparation & dosage**
Metformine (glucophage): 500 mg t.d.s after meal up to 2-3gm/d

**How it works**
- Decreases hepatic glucose output
- Increase glucose uptake from peripheral tissue and liver
- Lowers fasting glycaemia

**Attributes**

<table>
<thead>
<tr>
<th>How it works</th>
<th>Efficacy</th>
<th>Adverse events</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Gl side effects (reduced by initiating treatment at a low dose and gradually titrating)</td>
<td>Extensive experience</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lactic acidosis (extremely rare)</td>
<td>No weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindications CKD and Heart failure</td>
<td>No hypoglycemia</td>
</tr>
</tbody>
</table>

**Benefits**

- A1C reduced 1–1.5%
- Rare hypoglycemia
- High initial response rate
- Established safety profile
- No weight gain
- Favourable lipid profile
- Decreased macrovascular complications with monotherapy: UKPDS

**Risks**

- GI side effects in up to 50%
- Not tolerated in up to 20%
- Earlier loss of glucose control than TZDs
- Caution or contraindication if CrCl < 60 mL/min
- Lactic acidosis: very rare
- Discontinued at or prior to IV contrast and withheld for 48 hours post IV contrast
Thiazolidinedione

Preparation  | Pioglitazone  
Action  | Insulin sensitizer (PPAR-γ agonist)  
Indication  | T2DM (Obese & IR)  
Contraindication  | 1. Decompensated liver disease,  
2. CHF (NYHA 3,4)  

Attributes

How it works  | 1. Insulin sensitizers, they increase peripheral insulin action on skeletal muscle  
2. Decrease hepatic glucose production  

Efficacy  | High  
Disadvantage  | 1. Edema,  
2. Weight gain,  
3. Increases risk of CHF,  
4. Bone fracture,  
5. Increased risk of bladder cancer,  
6. High cost  

Advantage  | 1. No hypoglycemia  
2. Durability  
3. ↓TGs, ↑HDL-C  

Alpha-Glucosidase Inhibitors (Acarbose)

Action  | Competitive inhibitor of alpha glucosidase enzymes in small intestines; taken before meals  

Efficacy  | 1. Decrease fasting plasma glucose 20-30 mg/dl  
2. Decrease peak postprandial glucose 40-50 mg/dl  
3. No specific effect on lipids or blood pressure  
4. Reduce HbA1c 0.5-1.0%  

Other effects  | Flatulence  

Attributes

How it works  | An agent that inhibits an intestinal enzyme, resulting in reduced absorption of starches and sugars.  

Efficacy  | Modest  

Adverse events  | 1. GIT upset  
2. Flatulence  

Advantages  | 1. No body weight gain  
2. No hypoglycemia  
3. ↓Post-prandial glucose  

Phenylalanine derivatives

Repaglinide  (Novonorm)  

• Short pulse duration of action  
• Give after meal with capricious appetite  
• Full dose range (0.5-4 mg) with meals taken  

Incretin-based Therapies

Introduction  | 1. Incretin Hormones are hormones produced in GI tract in response to nutrients which in turn stimulates insulin secretion  
2. Predominant Hormones are GLP-1 (Glucagon-like peptide-1) and GIP (Glucose-dependent insulinotropic peptide)  
3. In patients with Type 2 diabetes, the incretin effect is either greatly impaired or absent, and it is assumed that this could contribute to the inability of these patients to adjust their insulin secretion to their needs  

Pharmacologic Approaches to Enhancing GLP-1 Action in Diabetes

How it works  | 1. Activates GLP-1 receptor  
2. ↑Insulin, ↓Glucagon  
3. ↓Gastric emptying  
4. ↑Satiety  

Attributes of GLP-1 Analogues

Efficacy  | High  
Disadvantage  | 1. GI  
2. ↑Pancreatitis  
3. Injectable  
4. High cost  

Advantage  | 1. Weight loss  
2. Low risk of hypoglycemia but relatively higher than DPP-4 inhibitors  
3. ↑βCell mass  
4. CV protection  

Attributes of DPP 4 inhibitors

Efficacy  | Moderate to High (Glucose Dependent Manner)  
Disadvantage  | 1. Pancreatitis  
2. High cost  
3. Well tolerated  

Management of DM during surgery

What to do?  | 1. Stop oral drugs or long acting insulin 2 days before & replaced by short acting insulin.  
2. Glucose + insulin + potassium solution should be infused during surgery.  
3. Post operatively maintain infusion till patient is able to eat.
**Introduction**

- Made in beta cells of the pancreas
- Moves glucose into cells
- Moves potassium into cells

**Indication**

1. Type 1 DM
2. Type 2 DM in special circumstances
   - Absolute: Pregnancy, DKA
   - Relative:
     - Uncontrolled by diet or oral drugs
     - Diabetic complications: renal failure
     - Intercurrent events: TB - infections - trauma – operations
3. Non diabetic use:
   - ttt of hyperkalemia,
   - combined insulin tolerance test for hypopituitarism, schizophrenia,
   - gastric function tests

**Source**

animal, human insulin by recombinant DNA technique

<table>
<thead>
<tr>
<th>Type</th>
<th>Preparation</th>
<th>Onset (H.)</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultra short insulin</td>
<td>Lispro Aspart (Novolog)</td>
<td>15 min</td>
<td>50 min</td>
<td>3-5h</td>
</tr>
<tr>
<td>Short acting &quot;soluble&quot;</td>
<td>-regular</td>
<td>1/2</td>
<td>2-4</td>
<td>6-8</td>
</tr>
<tr>
<td>intermediate acting insulin</td>
<td>NPH -Lente</td>
<td>2</td>
<td>4-8</td>
<td>12</td>
</tr>
<tr>
<td>Long acting insulin analogues</td>
<td>Glargine Detemir</td>
<td>2</td>
<td>Non</td>
<td>18-36</td>
</tr>
<tr>
<td>Biphasic (mixture)</td>
<td>-Mixtard</td>
<td>1/2</td>
<td>8-12</td>
<td>16-24</td>
</tr>
</tbody>
</table>

**Calculation of dose of insulin:**

1. Sliding scale technique
   - Start with 10 units Regular insulin before every meal and T dose by 5 units every day, then calculate the total daily dose.
2. Trial & error : Then calculate the total daily dose.

**Routines of administration**

1. SC injection
2. Intravenous: regular insulin
3. Insulin pump: insulin through a catheter in abdominal fat. (Given in severe cases, children, pregnant and renal transplant patient)

**Regimen**

A. Conventional:
   - 1. Single dose :
   - 2. 2 SC injection:
B. Multiple SC insulin injection 3-4 times/day or
C. Insulin pump in severe cases or in renal transplant

**Normal Pancreatic Function**

Basal: Beta cells secrete small amounts of insulin throughout the day.
Bolus: At mealtime, insulin is rapidly released in response to food.

**Insulin Preparations**

1. Rapid acting (lispro, asparte, glulisine)
2. Short acting (regular)
3. Intermediate acting (NPH)
4. Long acting
   - a. Ultralente
   - b. (Glargine/Detemir)

*given ONLY with syringes marked in "units"*

<table>
<thead>
<tr>
<th>Rapid acting</th>
<th>Short acting</th>
<th>Intermediate</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH, Lente (chemicals added. Cloudy)</td>
<td>0.5 to 1 hour</td>
<td>1 – 4 hours</td>
<td></td>
</tr>
<tr>
<td>Glargine/Lantus or detemir/levevir</td>
<td>15-30” minutes</td>
<td>2 – 4 hours</td>
<td>4 – 12 hours</td>
</tr>
<tr>
<td>Onset</td>
<td>Peak</td>
<td>Duration</td>
<td></td>
</tr>
<tr>
<td>“15-30” minutes</td>
<td>1 - 2 hours</td>
<td>3 – 4 hours</td>
<td></td>
</tr>
<tr>
<td>0.5 to 1 hour</td>
<td>2 – 4 hours</td>
<td>6 – 8 hours</td>
<td>18 – 24 hours</td>
</tr>
<tr>
<td>1 – 4 hours</td>
<td>4 – 12 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 – 4 hours</td>
<td>6 – 8 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine/Lantus or detemir/levevir</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
  - Cannot be diluted or mixed in syringe with any other insulin
  - Slow, steady release
  - Daily dosing [usually at bedtime]
  - Refrigerated or tosses every 14 days
<table>
<thead>
<tr>
<th>Combination insulin</th>
<th>70/30 (70% NPH and 30% regular)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Humolog 70/30 (Humolog and regular)</td>
</tr>
<tr>
<td></td>
<td>Fewer injections</td>
</tr>
<tr>
<td></td>
<td>Rotate sites to decrease lipodystrophy</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Complications of insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypoglycemia &amp; hypoglycemic coma</td>
</tr>
<tr>
<td>2. Insulin resistance:</td>
</tr>
<tr>
<td>- Definition: ↑↑ daily insulin requirements &gt; 200 IU in absence of conditions ass. with ↑↑ insulin demand (infection – pregnancy…)</td>
</tr>
<tr>
<td>- Causes:</td>
</tr>
<tr>
<td>a. Obesity : commonest cause for mild resistance</td>
</tr>
<tr>
<td>b. Antibodies against insulin preparations</td>
</tr>
<tr>
<td>c. Antibodies against insulin receptors</td>
</tr>
<tr>
<td>- Treatment: MC or human insulin, cortisone, plasma exchange</td>
</tr>
<tr>
<td>3. Insulin edema : mild LL edema (salt &amp; water retention)</td>
</tr>
<tr>
<td>4. Insulin lipodystrophy:</td>
</tr>
<tr>
<td>- Insulin lipoatrophy : change to purified or human insulin</td>
</tr>
<tr>
<td>- Insulin lipohypertrophy: (insulin tumor): change site of injection</td>
</tr>
<tr>
<td>5. Insulin Allergy : use monocomponent or human insulin</td>
</tr>
<tr>
<td>6. Acute neuropathy, Blurring of vision &amp; Weight gain</td>
</tr>
<tr>
<td>7. Smoggy effect:</td>
</tr>
<tr>
<td>- Nocturnal hypoglycemia: (night sweats, night mares &amp; morning headache)</td>
</tr>
<tr>
<td>- This causes rebound morning hyperglycemia</td>
</tr>
<tr>
<td>- tills by ↓ insulin dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Barriers to insulin therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight gain</td>
</tr>
<tr>
<td>Social embarrassmet</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
</tr>
<tr>
<td>Lifestyle changes</td>
</tr>
<tr>
<td>Painful injections</td>
</tr>
<tr>
<td>Feelings of failure/guilt</td>
</tr>
<tr>
<td>Become more ill; disease progression</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Patients factors</th>
<th>Physician factors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fear of patients’ anger and alienation; losing patients</td>
</tr>
<tr>
<td></td>
<td>Concern over compliance</td>
</tr>
<tr>
<td></td>
<td>Burden of additional training or dealing with crises during transition</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
</tr>
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