Chapter 17. Antidiabetic Drugs

Syllabus:
- Insulin and its preparations
- **Sulfonyl Ureas**: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride.
- **Biguanides**: Metformin.
- **Thiazolidinediones**: Pioglitazone, Rosiglitazone.
- **Meglitinides**: Repaglinide, Nateglinide.
- **Glucosidase inhibitors**: Acrabose, Voglibose

Pharmacology Lectures:
- Diabetes Meletus: [https://youtu.be/G_1QrQDMouM](https://youtu.be/G_1QrQDMouM)
- Oral antidiabetic Drugs: [https://youtu.be/s1eiqxdkZrg](https://youtu.be/s1eiqxdkZrg)
- Sulphonylureas: [https://youtu.be/p9ZJeWvTHoQ](https://youtu.be/p9ZJeWvTHoQ)
- DPP4 Inhibitors and Thiazolidinedione: [https://youtu.be/vK3TQ0MvRmQ](https://youtu.be/vK3TQ0MvRmQ)
- Biguanides and Acarbose: [https://youtu.be/cWUwBGqUOwY](https://youtu.be/cWUwBGqUOwY)

17.1. DIABETES MELETUS

Diabetes mellitus (DM), is a group of heterogenous metabolic diseases in which there are high blood sugar levels (hyperglycemia) over a prolonged period due to defect in insulin formation, secretion, and action.

DM is also known as Metabolic syndrome, Syndrome X or Insulin resistance syndrome.

Characterized by:
- Hyperglycemia (fasting blood glucose >7 mmol/L; >120 mg/dL)
- Altered carbohydrate metabolism
- Altered protein and Lipid metabolism

Symptoms:
- Polyurea (Frequent Urination)
- Glycosuria (Glucose in Urine)
- Polydipsia (Excessive Thirst)
- Polyphagia (Excessive Hunger)
- Lethargy, Fatigue

[www.youtube.com/pharmacologyconceptsbyrajeshchoudhary](http://www.youtube.com/pharmacologyconceptsbyrajeshchoudhary)
Types

➢ I. TYPE 1 DIABETES MELLITUS (10%)
   ➢ (Earlier called Insulin-dependent (IDDM), or juvenile-onset diabetes)
   ➢ Type IA DM: Immune-mediated
   ➢ Type IB DM: Idiopathic

➢ II. TYPE 2 DIABETES MELLITUS (80%)
   ➢ (earlier called non-insulin-dependent (NIDDM), or maturity-onset diabetes)

➢ III. GESTATIONAL DIABETES MELLITUS (4%)

➢ IV. OTHER SPECIFIC TYPES OF DIABETES (6-10%)

TYPE 1 DIABETES

➢ Earlier called Insulin-dependent (IDDM), or juvenile-onset diabetes (JOD)

➢ Account for 10% cases

➢ Usually Occurs in non-obese person before the age of 30 Years

➢ They are absolute requirement of insulin replacement as a treatment.

➢ Lack of both insulin release phase

➢ Beta-cells fails to respond to normal stimuli for insulin release

➢ As per new classification, neither age nor insulin dependence are considered as absolute criteria. So further Type I DM is can be classified into two subtypes: A. Type IA and B. Type IB

A. Type IA (Immune Mediate) Diabetes Mellitus:

➢ This type is characterized by Autoimmune Destruction of Beta-Cells which usually leads to Insulin Deficiency (Reduction in Insulin Production)

B. Type IB (Idiopathic Mediated) Diabetes Mellitus

➢ This type is characterized by insulin deficiency with tendency to develop ketosis but these patientsvare negative for autoimmune markers.

TYPE 2 DIABETES

➢ Earlier called non-Insulin-dependent (NIDDM), or maturity-onset diabetes (MOD)

➢ Account for 80% cases

➢ Usually Occurs in older individuals and obese adolescent children.
Many Type II DM patients require Insulin to prevent hyperglycemia, and ketosis and thus are not truly non-insulin dependent.

The basic metabolic defect in type II DM is either impaired insulin secretion and or insulin resistance.

17.2. INSULIN AND ITS PREPARATIONS

Isolated in 1921 by Banting & Best and used clinically in 1922.

Amino acid sequences of insulin (51 amino acid) were determined by Sanger’s Group in Cambridge in 1955.

Made up two polypeptide chains-

- A chain (Acidic)- 21 amino acid
- B Chain (Basic)- 30 amino acids

Chain A and B are linked together by two disulphide bridge [A7 Cys-B7 Cys and A20 Cys-B19 Cys]

**Biosynthesis**: synthesis within the pancreatic beta cell from proinsulin (single chain 86 amino acids).

**Propreinsulin (RER)** ➔ **Preinsulin (Golgi apparatus)** ➔ **Insulin**
Effects on Metabolism

<table>
<thead>
<tr>
<th>Type of metabolism</th>
<th>Liver cells</th>
<th>Fat cells</th>
<th>Muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate metabolism</td>
<td>↓ Gluconeogenesis</td>
<td>↑ Glucose uptake</td>
<td>↑ Glucose uptake</td>
</tr>
<tr>
<td></td>
<td>↓ Glycogenolysis</td>
<td>↑ Glycerol synthesis</td>
<td>↑ Glycogenolysis</td>
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<tr>
<td></td>
<td>↑ Glycolysis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fat metabolism</td>
<td>↑ Lipogenesis</td>
<td>↑ Synthesis of triglycerides</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>↓ Lipolysis</td>
<td>↑ Fatty acid synthesis</td>
<td>-</td>
</tr>
<tr>
<td>Protein metabolism</td>
<td>↓ Protein breakdown</td>
<td>-</td>
<td>↑ Amino acid uptake</td>
</tr>
</tbody>
</table>

Preparations

<table>
<thead>
<tr>
<th>Category/Name of Insulin</th>
<th>Brand Name (manufacturer)</th>
<th>Preparation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Lispro</td>
<td>Humalog (Lilly)</td>
<td>Vial, cartridge, disposable pen</td>
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<tr>
<td>Insulin Aspart</td>
<td>Novolog (Novo Nordisk)</td>
<td>Vial, cartridge, disposable pen</td>
</tr>
<tr>
<td>Insulin Glulisine</td>
<td>Apidra (Sanofi-Aventis)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td>Technosphere insulin</td>
<td>Afreeza</td>
<td>Inhaler</td>
</tr>
<tr>
<td>Short-Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Human</td>
<td>Humulin R (Lilly)</td>
<td>Vial</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category/Name of Insulin</td>
<td>Brand Name (manufacturer)</td>
<td>Preparation(s)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>NPH Human</td>
<td>Humulin N (Lilly)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td></td>
<td>Novolin N (Novo Nordisk)</td>
<td>Vial</td>
</tr>
<tr>
<td>Long-Acting</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Detemir</td>
<td>Levemir (Novo Nordisk)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td>Insulin Glargine</td>
<td>Lantus (Sanofi-Aventis)</td>
<td>Vial, cartridge, disposable pen</td>
</tr>
<tr>
<td></td>
<td>Basaglar (Lilly)</td>
<td>Basaglar is only available as a disposable pen</td>
</tr>
<tr>
<td></td>
<td>Toujeo (Sanofi-Aventis)</td>
<td>Toujeo is only available as a disposable pen</td>
</tr>
<tr>
<td>Insulin Degludec</td>
<td>Tresiba (Novo Nordisk)</td>
<td>Disposable pen</td>
</tr>
<tr>
<td>Insulin Mixtures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH/Regular (70%/30%)</td>
<td>Humulin 70/30 (Lilly)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td></td>
<td>Novolin 70/30 (Novo Nordisk)</td>
<td>Vial</td>
</tr>
<tr>
<td>Protamine/Lispro (50%/50%)</td>
<td>Humalog Mix 50/50(Lilly)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td>Protamine/Lispro (75%/25%)</td>
<td>Humalog Mix 75/25(Lilly)</td>
<td>Vial, disposable pen</td>
</tr>
<tr>
<td>Protamine/Aspart (70/30)</td>
<td>Novolog Mix 70/30 (Novo Nordisk)</td>
<td>Vial, disposable pen</td>
</tr>
</tbody>
</table>

17.3 MEDICINAL CHEMISTRY OF ORAL ANTIDIABETIC DRUGS

1. Sulfonylureas

**SAR:**

![Basic Ring of Sulfonylureas](image)

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www.youtube.com/pharmacologyconceptsbyrajeshchoudhary
www.pharmacyconcepts.in
Benzene ring contain substitution at para position.

- R- -CH₃, -COCH₃, -NH₂, -Cl, -Br, -CF₃, and dithiomethyl enhance the antihyperglycemic activity. Eg. Chlorpropamide > Tolbutamide

![Tolbutamide](image1)

![Chlorpropamide](image2)

- R- aryl carboxamidoalkyl (second-generation sulphonylureas, such as glibenclamide), the activity was found to be enhanced further
Glimepiride

- R1- the size of N-terminal is the most important for the lipophilicity and activity. N methyl or ethyl has show no activity, while N-propyl and higher homologues were found to be active upto 11-C atom. N-substitution contains more than 12-C atom lost their activity.

Selected Drugs: Tolbutamide*, Chlorpropamide, Glipizide, Glimepiride

Mechanism of Action

- Sulfonylureas stimulate the release of insulin form pancreas. They act on ‘sulfonylurea receptors’ (SUR1) on the pancreatic β cell membrane → cause depolarization by reducing conductance of ATP sensitive K+ channels→ enhances Ca2+ influx degranulation→ Stimulate the rate of insulin secretion at any glucose concentration.
- The sulfonylureas primarily augment the 2nd phase insulin secretion with little effect on the 1st phase
Uses:

✓ Treatment of Type-2 Diabetes
✓ Tolbutamide has some diuretic action and tolbutamide can be used in the diagnosis of insulinoma

A) Tolbutamide

1-butyl-3-(4-methyl phenyl) sulfonyl urea

Synthesis:
B) Chlorpropamide

1-propyl-3-(4-chloro phenyl) sulfonyl urea

C) Glipizide

N-[2-[4-(cyclohexyl carbamoyl sulfamoyl) phenyl] ethyl]-5-methyl pyrazine-2-carboxamide

D) Glimepiride

4-ethyl-3-methyl-N-[2-[4-[(4-methyl cyclohexyl) carbamoyl sulfamoyl]phenyl]ethyl]-5-oxo-2H-pyrrole-1-carboxamide
2. Biguanides

*Phenformin is currently not in used due to high risk of lactic acidosis.

A) Metformin

MOA:
Biguanides do not cause insulin release, but for the action insulin is essential; thus they not effective in type-1 diabetes. Biguanides activate the **AMP-dependent protein kinase (AMPK)** to play a crucial role in mediating the actions of metformin, the key features of which are:

a) decrease the hepatic gluconeogenesis and glucose output from liver (MAJOR ACTION)

b) improve the peripheral glucose utilization by reducing insulin resistance.

c) enhance the cellular respiration

Uses: Preferred (1st choice drug) for treatment of type-2 diabetes.

3. Thiazolidinediones (PPARy Agonist)

Pioglitazone and Rosiglitazone are the thiazolidinediones derivatives. Rosiglitazone is currently banned in India since 2010 due to high risk of in risk of myocardial infarction, CHF, stroke and death

MOA: thiazolidinediones are the selective nuclear peroxisome proliferator-activated receptor (PPARy) agonist, which is expressed mainly in fat cells, but also in muscle and some other cells.
➢ It enhances the transcription of several insulin responsive genes.
➢ Reverse the insulin resistance by enhancing GLUT4 expression and translocation.
➢ Improve the Entry of glucose into muscle and fat cells.
➢ Supress the hepatic gluconeogenesis
➢ Lipolysis and plasma fatty acid levels are reduced. Fatty tissue is a major site of their action.

**Uses:**
✓ Pioglitazone is indicated in type 2 DM, but not in type 1 DM.
✓ It reduces blood glucose and HbA1c (by 0.5–1.2%) without increasing circulating insulin

**A) Pioglitazone**

![Pioglitazone structure](image)

5-[[4-[2-(5-ethyl pyridin-2-yl)ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione

**B) Rosiglitazone.**

![Rosiglitazone structure](image)

5-[[4-[2-[methyl(pyridin-2-yl)amino]ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione
4. Meglitinides

Repaglinide and Nateglinide are meglitinide analogue oral hypoglycaemic is designed to normalise mealtime glucose excursions. Though not a sulfonylurea, it acts in an analogous manner by binding to SUR → closure of ATP dependent K+ channels → depolarisation → insulin release. It is generally taken before each major meals to control postprandial hyperglycaemia.

A) Repaglinide

![Chemical structure of Repaglinide]

2-ethoxy-4-[[2-[(1S)-3-methyl-1-(2-piperidin-1-ylphenyl)butyl]amino]-2-oxoethyl]benzoic acid

MOA: KATP channel blockers

Uses: Treatment of type 2 diabetics who suffer pronounced post prandial hyperglycaemia, or to supplement metformin/long-acting insulin. It is contraindicated in liver disease condition.

B) Nateglinide

![Chemical structure of Nateglinide]

(2R)-3-phenyl-2-[(4-propan-2-yl cyclohexanecarbonyl)amino]propanoic acid
**MOA:** It is a D-phenylalanine derivative which principally stimulates the 1st phase insulin secretion by closing β cell KATP channels resulting in faster onset and shorter lasting hypoglycaemia than repaglinide.

**Uses:** It is taken 10 min before meal, it limits postprandial hyperglycaemia in type 2 diabetics without producing late phase hypoglycaemia.

**5. Alfa Glucosidase inhibitors**

They reversibly inhibit α-glucosidases, which is responsible for digestion of carbohydrates in the brush border of small intestine mucosa. It slows down and decreases digestion and absorption of polysaccharides (starch, etc.) and sucrose.

**A) Acarbose**

![Acarbose structure](image)

Uses: Acarbose (25-50 mg/day, start with low dose) is used in the treatment of Type-2 diabeted used alone or along with other oral antidiabetic drugs and/or insulin.

**B) Voglibose**

![Voglibose structure](image)

3,4-dideoxy

(1S,2S,3R,4S,5S)-5-(1,3-dihydroxypropan-2-ylamino)-1-(hydroxymethyl)cyclohexane-1,2,3,4-tetrol

www.youtube.com/pharmacologyconceptsbyrajeshehoudhary
www.pharmacyconcepts.in
**Uses:** Used in the treatment of Type 2 diabetes mellitus (dose 200-300 ug three time in a day) alone or along with sulfonylureas or insulin.