HYPOGLYCEMIC AGENTS

Diabetes mellitus is a chronic metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with characteristic symptoms such as thirst, polyuria, blurring of vision and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death.

Classification of Diabetes mellitus

   Diabetes may be classified as

i) Type - I Diabetes mellitus
ii) Type - II Diabetes mellitus
iii) Type - 1.5 Diabetes mellitus
iv) Gestational Diabetes

INSULIN

Peptides hormones are secreted by the pancreas occupy a central role in the regulation of metabolism of carbohydrates, lipids and amino acids. They are Insulin, Glucagon and Somatostatin. Insulin is the primary hormone which is responsible for controlling the storage and utilization of cellular nutrients. It activates the transport system and the intracellular utilization and storage of glucose, amino acids and fatty acids. Insulin inhibits catabolic processes such as the breakdown of glycogen, fat and protein, whereas the overall effect of insulin is hypoglycaemic. The other pancreatic hormone Glucagon mobilize glucose from its stores and causes hyperglycaemia. The third pancreatic hormone Somatostatin, inhibit secretion of both Insulin and Glucagon.

Deficiency of effective insulin in the body causes a disease called diabetes mellitus (meaning in Greek is excessive thirst) which alters the metabolism of lipids, carbohydrates and proteins. This results in hyperglycaemia and glycosuria. Insulin was purified and crystallized by J.J.Abel in 1926. The amino acid sequence of the hormone was established by F.Sanger and the co-workers in 1955. Its total synthesis was achieved by several groups in 1970’s. Hodgkin and co-workers established the three dimensional structure of Insulin. Recently the cloning of human Insulin gene and its transfer into bacteria Escherichia coli have been achieved, it is now produced by recombinant DNA technology.
Animal and Human Insulin

<table>
<thead>
<tr>
<th>Species</th>
<th>Chain A</th>
<th>Chain B 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Human</td>
<td>Thr</td>
<td>Ile</td>
</tr>
<tr>
<td>Porcine</td>
<td>Thr</td>
<td>Ile</td>
</tr>
<tr>
<td>Bovine</td>
<td>Ala</td>
<td>Val</td>
</tr>
</tbody>
</table>

Currently available Insulin Preparations

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Administration Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-acting Insulins</strong></td>
<td></td>
</tr>
<tr>
<td>Humalog (insulin lispro)</td>
<td>Insulin pen, vial or 1.5-mL and 3-mL pen cartridge</td>
</tr>
<tr>
<td>NovoLog (insulin aspart)</td>
<td>Insulin pen, vial or 3-mL pen cartridge</td>
</tr>
<tr>
<td>Apidra (insulin glulisine)</td>
<td>Vial</td>
</tr>
<tr>
<td><strong>Short-acting Insulins</strong></td>
<td></td>
</tr>
<tr>
<td>Humulin R (regular)</td>
<td>U-100, 10-mL vial</td>
</tr>
<tr>
<td>Available in: U-100 and U-500</td>
<td>U-500, 20-mL vial</td>
</tr>
</tbody>
</table>
Novolin R (regular) | Insulin pen, vial or 3-mL pen cartridge and InnoLet

**Intermediate-acting Insulins**

**NPH**

- Humulin N | Vial, prefilled pen
- Novolin N | Vial, prefilled pen, and InnoLet
- Lente | Lente
- Humulin L | Vial

**Long-acting Insulins**

- Humulin U (ultralente) | Vial
- Lantus (insulin glargine) | Vial

**Pre-mixed Insulins**

**Pre-mixed insulin analogs**

- Humalog Mix 75/25 (75% neutral protamine lispro, 25% lispro) | Vial, prefilled pen
- Novolog Mix 70/30 (70% aspart protamine suspension, 30% aspart) | Vial, prefilled pen, 3-mL pen cartridge

**NPH-regular combinations**

- Humulin 70/30 | Vial, prefilled pen
- Novolin 70/30 | Vial, pen cartridge, InnoLet
- Humulin 50/50 | Vial

**ORAL HYPOGLYCEMIC AGENTS**

Oral hypoglycemic agents are the drugs that lower blood glucose levels and are effective orally. The main disadvantage of insulin and its preparations is that they must be given by injection or inhalation. Hence, orally active drugs have always been searched.

**CLASSIFICATION**

i) Sulfonyl ureas.


ii) Biguanides: eg. Metformin, Phenformin, Buformin.

iv) Thiazolidinediones: eg. Pioglitazone.

v) α - Glucosidase inhibitors: eg. Acarbose, Miglitol, Voglibose.


vii) DPP-4 inhibitors: eg. Sitagliptin, Saxagliptin, Vildagliptin, Alogliptin.

viii) GLP-1 agonist: eg. Exenatide.

Miscellaneous: eg. Ciglitazone, Linogliride, Pirogliride, Palmoxivate sodium

**Tolbutamide (Rastinone)**

![Tolbutamide Molecular Structure]

**Chlorpropamide (Chloroformin)**

![Chlorpropamide Molecular Structure]

**Glibencamide (Daonil, Glinil)**

![Glibencamide Molecular Structure]


**Glipizide (Diaglip, Dibizide)**

![Glipizide Molecular Structure]
1-Cyclohexyl -3-[[p-\{2-(5-methyl pyrazine carboxamide) ethyl\} phenyl sulfanyl] urea

**Biguanides**

The general chemical structure of biguanide is follows.

\[
R_1 \begin{array}{c} \\
N - C - NH - C - NH_2 \\
R_2 \\
\end{array} 
\]

**Metformin (Riomet, Glumet)**

\[
\begin{array}{c} \\
H_3C - N - C - NH - C - NH_2 \\
\end{array}
\]

It is used to treat type II diabetes with an advantage of weight reduction and absence of significant hypoglycemia.