Type 2 diabetes mellitus is characterized by high plasma glucose resulting from a dynamic interaction between defects in insulin secretion and insulin action. K<sub>ATP</sub> channel plays a role in depolarization-response coupling and its genetic defects are associated with impaired insulin secretion.

In normal person, pancreatic β cells in the presence of >5.5 mM glucose will be depolarized and release insulin. The increase in carbohydrate metabolism leads to an increase in the ratio of ATP/ADP that leads to the closure of the ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels followed by depolarization. The membrane depolarization leads to the activation of voltage-dependent Ca<sup>2+</sup> channels. The Ca<sup>2+</sup> ion influx activates Ca<sup>2+</sup>-regulated exocytosis of insulin-containing secretory granules to fuse with the plasma membrane. The mechanism of depolarization response coupling is maintained by: (1) The Na<sup>+</sup>-K<sup>+</sup>-ATPase pump and open K<sub>ATP</sub> channels maintain the resting membrane potential. (2) K<sub>ATP</sub> channels close as a consequence of the increase in ATP/ADP ratio. (3) A depolarization of the cell membrane leads to the activation of voltage-dependent Ca<sup>2+</sup> channels. (4) The ensuing rise in the free intracellular concentration of Ca<sup>2+</sup> ([Ca<sup>2+</sup>]) initiates the release of insulin by exocytosis.

Figure 1 The control of insulin release from human pancreatic β cells (adapted from Aizawa et al., 1998).
**K⁺ Channels and Sulphonylurea Receptors**

The selective inhibition of $K_{ATP}$ channel with sulphonylureas will mimic the actions of glucose and promote insulin release, while diazoxide, and voltage-gated Ca²⁺ channel blockers, such as nifedipine, open $K_{ATP}$ channel and inhibit insulin secretion. $K_{ATP}$ channel complex in β cells composed of 2 interdependent different groups of subunits:

1. Kir6.2, a member of the inward rectifier K⁺ channel family, forms the K⁺-selective pore or tunnel. Kir6.2 shares ~70% homology with Kir6.1, consists of 390 amino acids, and has two α-helical transmembrane domains linked by a highly conserved sequence of amino acids homologous with the Por H5-region of voltage-gated K⁺ channels. Kir6.2 determines biophysical properties such as ion selectivity, rectification and gating of the complex.

2. SUR1, a high affinity 1581-amino acid sulphonylurea receptor, is a member of the superfamily of ATP-binding cassette (ABC) proteins that include the cystic fibrosis transmembrane conductance regulator (CFTR), and multi-drug resistance associated proteins. This superfamily shares common structure with numerous transmembrane sequences and nucleotide binding domains. Two closely related genes encode two sulphonylurea receptors, SUR1 and SUR2. Three splice variants of the SUR2 protein include SUR2A, SUR2B and SUR2C. SUR1 affects the trafficking and distribution of Kir6.2. The SUR1 gene consists of 39 exons and is clustered with the Kir6.2 gene, a single open reading frame lying immediately 3' of the SUR1 gene, separated by only 4.5 kilobase pairs. The gene location is on the short arm of chromosome 11.

The $K_{ATP}$ channel is an octameric complex formed by four Kir6.2 subunits coupled to four SUR1 subunits. $K_{ATP}$ channels in other tissues are octameric complexes of other Kir6.x and SUR proteins: cardiac Kir6.2 + SUR2A, smooth muscle Kir6.2 + SUR2B, and the smooth muscle nucleotide-activated channel Kir6.1 + SUR2B. The K⁺ channel is sensitive to adenine and guanosine nucleotides. ATP can activate Kir6.2, whereas either ADP or GDP binds one of the nucleotide-binding folds of SUR1 and antagonizes the effects of ATP. Therefore, SUR1 regulates Kir6.2 by conferring sensitivity to metabolic signals and to other pharmacological agents, such as diazoxide, somatostatin and the sulphonylureas.

Sulphonylureas, in addition to closing $K_{ATP}$ channels, inhibit the Na⁺-K⁺-ATPase and both inhibit and activate swell-activated Cl⁻ channels, potentiate Ca²⁺-dependent exocytosis in β cells. α-endsosulfine, a 13-kDa peptide ligand of sulphonylurea receptors, was expressed in muscle, brain and endocrine cells. It can stimulate insulin release through the inhibition of $K_{ATP}$ channels.

Pharmacological approaches of diabetes mellitus can be either monotherapy or in various combinations to improve glucose homeostasis via different modes of action (Fig. 3). Sulphonylureas stimulate insulin secretion. Biguanides promote glucose utilization and reduces hepatic glucose production. α-glucosidase inhibitors decelerate carbohydrate absorption from the gut, reduce postprandial glucose fluctuations and improve glycemic stability that can be used during pregnancy. Thiazolidinedione enhances cellular insulin action on glucose and lipid metabolism through its action on PPAR-γ.
Figure 2 The structure of ATP-sensitive K⁺ (K\textsubscript{ATP}) channels in pancreatic β cells (adapted from Dunne et al., 1999). (A) The key regulatory and pharmacological influences on K\textsubscript{ATP} channels. (B) The topology of the K⁺ channel subunit Kir6.2. (C) The topology of the SUR1 gene product. (D) The octameric structure of K\textsubscript{ATP} channel complex (Kir6.2–SUR1) × 4.

Figure 3 Sites of action of antidiabetic drugs (adapted from Scheen and Lefèbvre, 1998)
The selection of oral anti-hyperglycemic agents is based on both the pharmacological properties of the compounds (mode of action, efficacy, adverse effects, and safety profile) and the clinical characteristics of the patient (the degree of hyperglycemia, bodyweight, age, renal function, etc.).

(a) Mildly hyperglycemic patients should preferably be treated with metformin, acarbose or thiazolidinediones since they are not associated with any hypoglycemic risk.

(b) Moderately hyperglycemic patients, sulphonylureas should be preferred in nonobese patients while metformin, and probably also thiazolidinediones, should have priority in obese insulin-resistant type 2 diabetic patients.

(c) More severely hyperglycemic individuals should receive a sulphonylurea.

Figure 3 Stepwise treatments of type 2 diabetes (Adapted from Scheen and Lefebvre, 1998)
Table 1  Commercially available oral anti-hyperglycemic drugs

<table>
<thead>
<tr>
<th>Sulphonylureas</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
</tr>
<tr>
<td>carbutamide, tolazamide, tolbutamide,</td>
</tr>
<tr>
<td>chlorpropamide</td>
</tr>
<tr>
<td>Second generation</td>
</tr>
<tr>
<td>glibenclamide (glyburide), glipizide</td>
</tr>
<tr>
<td>(conventional and extended release),</td>
</tr>
<tr>
<td>gliclazide, gliclizide, glimepiride, etc.</td>
</tr>
<tr>
<td>Biguanides</td>
</tr>
<tr>
<td>metformin, phenformin</td>
</tr>
<tr>
<td>α-Glucosidase inhibitors</td>
</tr>
<tr>
<td>acarbose</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>rosiglitazone, pioglitazone</td>
</tr>
</tbody>
</table>

Sulphonylureas

Sulphonylureas essentially stimulate insulin secretion. Less than 60 - 70% of patients achieve good glycemic targets. Patients with high fasting plasma glucose and severe obesity usually have high initial failure rate. About 10% of those initially responders per year will fail to respond to subsequent treatment (secondary drug failure). The main adverse effect of sulphonylurea derivatives is hypoglycemia. This adverse effect is most often associated with chlorpropamide and glibenclamide. Other adverse effect includes weight gain of several kilograms, chlorpropamide-induced hyponatremia secondary to inappropriate anti-diuretic hormone activity, alcohol disulfiram-like facial flushing. Second-generation drugs (glibenclamide, glipizide, gliclazide, gliclizide, glimepiride) have shorter half-life and are preferred to first-generation drugs. Gliclizide is excreted via liver and is therefore preferred in patients with mild renal impairment. Glibenclamide should be avoided in patients with renal disease since it carries a higher risk of hypoglycemia. All initial dosages should be reduced by at least a half to avoid hypoglycemia especially in only mildly to moderately hyperglycemia. All sulphonylureas should be administered 30 minutes before meal to control early postprandial hyperglycemia. The secondary drug failure usually results from progressive β cell failure since sulphonylureas rely on insulin-producing capacity of β cells. Chlorpropamide and gliclazide have less secondary failure rates than glibenclamide or glipizide. Gliclazide has a favorable effect toward improving retinopathy since it can reduce thrombotic tendency, enhance fibrinolysis, and scavenge free radicals.

Metformin

Metformin does not stimulate insulin secretion, but enhanced both non-insulin-mediated and insulin-mediated glucose metabolism with unclear underlying mechanisms. Metformin decreases hepatic glucose output, stimulate peripheral glucose uptake and increase intestinal glucose use. Metformin can improve insulin sensitivity and reduce hyperinsulinemia and is indicated as a first-line antidiabetic drug in obese diabetic patients. Metformin has favorable action on biochemical
disorders associated with insulin resistance, such as high triglyceride levels, low levels of high-density lipoprotein (HDL) and high plasminogen activator inhibitor-1 (PAI-1) levels. Metformin does not cause bodyweight gain, reduces plasma insulin levels and only rarely causes hypoglycemia. The drug should be taken with meals to improve digestive tolerance. The major potential adverse effect is lactic acidosis. Metformin should be avoided in patients with decreased renal function, liver disease and cardiac or respiratory insufficiency. Minor adverse effects include abdominal discomfort, nausea and loose bowel actions during the initiation of therapy, malabsorption of cyanocobalamin (vitamin B12) and folic acid with long term use.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors such as acarbose and voglibose competitively inhibit small intestinal α-glucosidase enzymes. This enzyme normally hydrolyzes non-absorbable complex carbohydrates into absorbable monosaccharides including glucose. The enzyme blockade leads to a delayed rising in postprandial plasma glucose, and consequently plasma insulin concentrations. The treatment can improve HbA1c levels, reduce bodyweight, and decrease the incidence of hypoglycemic episodes. Since this class of drug is not absorbed, systemic adverse effects rarely occur but the major adverse effect is dose-related and transient gastrointestinal intolerance (flatulence, soft stools or diarrhea, mild abdominal pain), due to osmotic effect and bacterial fermentation of undigested carbohydrates in the distal bowel. The dosage should be gradually increased to limit gastrointestinal symptoms.

Thiazolidinediones

Thiazolidinediones include pioglitazone and rosiglitazone are known as “insulin sensitizer”. This class of drug does not stimulate insulin secretion, but enhances insulin action and promotes glucose utilization in peripheral tissues by stimulating non-oxidative glucose metabolism in muscle, and suppressing gluconeogenesis in the liver. Drug action is attributed to the stimulation of nuclear receptors, peroxisome proliferator activated receptors (PPAR-γ) that in turn enhance the expression of a number of genes encoding proteins involved in glucose and lipid metabolisms. This class of drug can improve insulin resistance, glucose tolerance without inducing bodyweight gain or hypoglycemia, lipid abnormalities, arterial hypertension. Cardiac output and stroke volume are enhanced secondary to a decrease in mean arterial pressure and peripheral vascular resistance. The onset of action for initial plasma glucose- and insulin-lowering effects is 1 to 4 weeks while the maximal responses (mean reduction of 20% in plasma glucose concentrations and of 30% in plasma insulin levels) is 6 to 8 weeks.

Repaglinide

Repaglinide is a carbamoylmethyl benzoic acid derivative that reduces blood glucose by stimulating insulin release from pancreatic β-cells in similar fashion to sulphonylureas. Repaglinide is different from sulphonylureas in the structure, binding profile, short duration of action, and mode of excretion. The drug dosage and meal timetable can be varied and customized before each meal. The overall incidence of
hypo glycemia was similar to that of sulphonylureas, but with less severity due to its short duration of action.

**Therapeutic Strategy in Type 2 Diabetes**

**First Choice Drug Treatment**

1. Diet treatment will be started for 1-3 months.
2. Treatment with one of the 4 available oral anti-hyperglycemic drugs when diet treatment fails.
   2.1 Obese patients with a fasting plasma glucose level of 7-7.8 mmol/L (126-140 mg/dL) should be treated with metformin since obese people are often hyperinsulinemic as well as insulin-resistant and therefore do not require further sulphonylurea-induced stimulation of insulin secretion. An alternative choice in this group can be a thiazolidinedione in those with severe insulin resistance.
   2.2 Non-obese or modestly overweight patients with fasting plasma glucose between 7.8 and 11.1 mmol/L (140 and 200 mg/dL) should be treated with low dose sulphonylureas that can stimulate insulin release and promote bodyweight gain.
   2.3 Severely hyperglycemic patients [fasting plasma glucose exceeding 11.1 mmol/L (200 mg/dL)] should be treated with a sulphonylurea in the first instance.
   2.4 Modest fasting hyperglycemia with high postprandial glucose or elderly patient can be treated with acarbose as monotherapy.

**References:**