A Review Article Of Anti-Diabetic Drug For Type-I And Type-II Diabetes.

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Abstract: -
Diabetes mellitus is one of the world’s major diseases and is the third leading cause of death in the United States after heart disease and cancer. Diabetes mellitus is a condition characterized by the body’s loss of control over blood sugar. Type-I and Type-II Diabetes are the Two clinical forms of diabetes mellitus. An expanding range of differently acting oral anti-diabetic agents provides new choices for type 2 patients. T2DM is a major contributor to the very large rise in the rate of non-communicable diseases affecting developed as well as developing nations. This review considers the attributes and limitations of these agents, and their positioning in the treatment process and current management principles, including the spectrum of medications that are currently used for pharmacologic management, for lowering the elevated blood glucose in T2DM.

Keywords: Anti-diabetic drugs, type-II diabetes, clinical management, chronic, insulin.

Introduction
The prevalence of diabetes mellitus continues to rise and is set to reach 300 million people worldwide by the year 2025 (figure 1).

1. In most European countries 3–5% of the adult population has diabetes, with the vast majority (> 95%) of these patients having type 2 (non-insulin dependent) diabetes.

Macro vascular complications are commonplace amongst diabetic patients, particularly those with type 2 diabetes (table 1).

The basic defects in Type 2 diabetes consist of (1) Insulin deficiency (2) Insulin resistance and (3) increased hepatic glucose production (HGP) leading to glucotoxicity, beta cell exhaustion and finally beta cell failure. The treatment strategies to overcome these defects are:
1) Modified meal Plan
2) Exercise
3) Blood glucose lowering drugs and
4) Insulin

The current oral blood glucose lowering agents and dietary measures only partially correct the multiple metabolic defects in NIDDM with insulin resistance remaining relatively impervious to treatment Hypoglycemia and secondary failure are common with presently available Sulphonylurea and hence the need for newer blood glucose lowering drugs.
Main causes of diabetes mellitus are:
- Genetic defect of beta cell function.
- Genetic defect in insulin action.
- Disease of the exocrine pancreas.

Endocrinopathies, i.e., changes in hormonal secretion and, Drugs or chemical induced.

**Type of diabetes mellitus**

1) Insulin dependant or juvenile-onset diabetes mellitus (Type-I)
2) Non insulin dependant or maturity-onset diabetes (Type-II)

**Type-I:**

Insulin dependent diabetes mellitus (IDDM) i.e. patients require periodic doses of insulin it can occur at any age, commonly occurs in children, Characterized by the marked inability of the pancreas to secrete insulin because of autoimmune destruction of the beta cells. Kidney malfunctioning, nerve impairment, cardiovascular disease and retinal degeneration occur.

**Type-I I:**

Non-insulin dependent diabetes mellitus (NIDDM). It accounts for about 90% of the diagnosed case of diabetes and affects 18% of the population over 65 years of age. Insulin receptors on insulin responsive cells do not respond normally to insulin and are therefore called as “insulin resistant”, thereby increasing blood glucose level.

**Gestational diabetes:**

Gestational diabetes is ‘any degree of glucose intolerance with onset or first recognition during pregnancy.

**Insulin:**

Insulin was discovered in 1921 by Banding and Best Who demonstrated the hypoglycaemic action of an extract of pancreas prepared after degeneration of the exocrine part due to ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and chemical structure in 1956 by Sanger.

Insulin is a two polypeptide chain having 51 AA an MW 6000. Chain A has a 21 AA while chain B has 30 AA.

<table>
<thead>
<tr>
<th>Species</th>
<th>A-chain</th>
<th>B-chain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8th AA</td>
<td>10th AA</td>
</tr>
<tr>
<td>Human</td>
<td>THR</td>
<td>ILEU</td>
</tr>
<tr>
<td>Pork</td>
<td>THR</td>
<td>ILEU</td>
</tr>
<tr>
<td>Beef</td>
<td>ALA</td>
<td>VAL</td>
</tr>
</tbody>
</table>

The clinical diagnosis of diabetes is reliant on either one of the four plasma glucose (PG) criteria: elevated (i) fasting plasma glucose (FPG) (>126 mg/dL), (ii) 2 h PG during a 75-g oral glucose tolerance test (OGTT) (>200 mg/dL), (iii) random PG (>200 mg/dL) with classic signs and symptoms of hyperglycemia, or (iv) hemoglobin A1C level >6.5%. Recent American Diabetes Association (ADA) guidelines have advocated that no one test may be preferred over another for diagnosis. The recommendation is to test all adults beginning at age 45 years, regardless of
body weight, and to test asymptomatic adults of any age who are overweight or obese, present with a diagnostic symptom, and have at least an additional risk factor for development of diabetes.

The agents which are given orally to reduce the blood glucose levels in diabetic patients are called anti-diabetic agents.

**Classification Of Anti diabetic drugs :-**

**Insulins: - (Parenteral)**
- Regular insulin
- NPH insulin
- Aspart insulin
- Protamine aspart insulin
- Degludec
- Detemir insulin

**Sulfonylureas:**
- First Generation: - Acetohexamide, Chlorpropamide, Tolazamide, Tolbutamide.
- Second Generation: - Glibenclamide, Glipizide, Gliclazide, Glimepiride.

**Meglitinide:**
- Rapaglinide
- Nateglinide

**Dipeptidyl peptidase-4 inhibitors:** - All gliptin category
- Sitagliptin
- Linagliptin
- Vildagliptin
- Saxagliptin
- Teneligliptin
- Alogliptin

**Alpha Glucosidase 4 inhibitors:**
- Voglibose
- Miglitol
- Acarbose

**Biguanide:**
- Metformin
- Phenformin
- Buformin

**Thiazolidinedione:**
- Pioglitazone
- Rosiglitazone

**Miscellaneous:**
- i) Sod. Glucose cotransport-2 (SGLT-2) inhibitor: - Dapagliflozin, Canagliflozin
- ii) Dopamine D2 agonist: - Bromocriptine
### Table: Oral Anti Diabetic Drugs.

<table>
<thead>
<tr>
<th>Name</th>
<th>Daily Dosage (mg)</th>
<th>Duration of Action</th>
<th>Activity of metabolites</th>
<th>Main Elimination route</th>
<th>Tablet Strength (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(a) Sulphonylureas</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>100–500</td>
<td>Long</td>
<td>Active</td>
<td>Urine &gt; 90%</td>
<td>100, 250</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>2.5–15</td>
<td>Intermediate–long</td>
<td>Active</td>
<td>Bile &gt; 50%</td>
<td>2.5, 5.0 (scored)</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>1–6</td>
<td>Intermediate–long</td>
<td>Active</td>
<td>Urine ~60%</td>
<td>1,2,3,4 (all scored)</td>
</tr>
<tr>
<td><em>(b) Gliclazide MR</em></td>
<td>30–120</td>
<td>Intermediate–long</td>
<td>Inactive</td>
<td>Urine ~65%</td>
<td>30 (scored)</td>
</tr>
<tr>
<td><em>(c) Gliclazide</em></td>
<td>40–320</td>
<td>Intermediate</td>
<td>Inactive</td>
<td>Urine ~65%</td>
<td>80 (scored)</td>
</tr>
<tr>
<td>Glipizide</td>
<td>2.5–20</td>
<td>Short–intermediate</td>
<td>Inactive</td>
<td>Urine ~70%</td>
<td>2.5, 5.0 (scored)</td>
</tr>
<tr>
<td>Gliquidone</td>
<td>15–180</td>
<td>Short–intermediate</td>
<td>Inactive</td>
<td>Bile ~95%</td>
<td>30 (scored)</td>
</tr>
<tr>
<td><em>(c) Tolbutamide</em></td>
<td>500–2000</td>
<td>Short</td>
<td>Inactive</td>
<td>Urine ~100%</td>
<td>500</td>
</tr>
<tr>
<td><strong>(c) Meglitinides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5–16</td>
<td>Very short</td>
<td>Inactive</td>
<td>Bile ~90%</td>
<td>0.5, 1, 2</td>
</tr>
<tr>
<td><em>(d) Nateglinide</em></td>
<td>60–540</td>
<td>Very short</td>
<td>Inactive</td>
<td>Urine ~80%</td>
<td>60, 120, 180</td>
</tr>
<tr>
<td><strong>Biguanide</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(c) Metformin</em></td>
<td>500–3,000</td>
<td>Short–intermediate</td>
<td>Not metabolized</td>
<td>Urine ~100%</td>
<td>500, 850</td>
</tr>
<tr>
<td><strong>(d) Thiazolidinedione’s</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>4–8</td>
<td>Intermediate–long</td>
<td>Very weakly active</td>
<td>Urine ~65%</td>
<td>4, 8</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>15–30</td>
<td>Intermediate–long</td>
<td>Active</td>
<td>Bile &gt; 70%</td>
<td>15, 30</td>
</tr>
<tr>
<td><strong>Alpha-Glucosidase inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>(c) Acarbose</em></td>
<td>50–300</td>
<td>Short</td>
<td>(e) inactive</td>
<td>(e) Urine ~35%</td>
<td>50, 100</td>
</tr>
</tbody>
</table>

**Key:**
- * = very short < 6 hour; short < 12 hour; intermediate 12–24 hour; long 18 – > 24 hour
- a = large dosages should be divided and related to meal pattern
- b = gliclazide MR (Diamicron MR) is a modified release formulation: 30 mg of the MR formulation is approximately therapeutically equivalent to 80 mg of standard Gliclazide
- c = should be taken immediately before meals
- d = first-line drug therapy excluded in UK: use in combination therapy only
- e = degraded mainly in intestine. Some metabolites absorbed but very little parent drug absorbed
Insulin: Insulin is an essential peptide hormone secreted by the β cells of the pancreatic islets of Langerhans. It helps your body turn food into energy and controls your blood sugar levels. If you have diabetes, your body can’t make enough insulin or can’t use it properly.

Synthesis: -

Insulin consists of two polypeptide chains, an A chain (21-AA) and a B chain (30-AA) covalently linked by two inter-chain disulfide bridges. There is a third, intra-chain disulfide bridge.
Insulin initiates its action by binding to a glycoprotein receptor on the surface of the cell. This receptor consists of an alpha-subunit, which binds the hormone, and a beta-subunit, which is an insulin-stimulated, tyrosine-specific protein kinase. Activation of this kinase is believed to generate a signal that eventually results in insulin’s action on glucose, lipid, and protein metabolism.

**Sulfonylureas:**

Sulfonylureas are the oldest class of oral ant diabetic medication dating back to the 1950s. All sulfonylureas contain a phenyl-sulfonyl-urea structure, which exerts the hypoglycemic effect. Patients with type II diabetes mellitus use sulfonylureas as monotherapy or in combination with other oral or injectable medications. Sulfonylureas are divided into first-generation and second-generation.

**Mechanism:**

Sulfonylureas bind to and inhibit the **ATP-sensitive potassium channels (K)** on the pancreatic beta cells. As a result, potassium efflux decreases, and the beta-cell membrane depolarizes. Membrane depolarization causes calcium channels to open, leading to calcium influx and increased intracellular calcium, which stimulates insulin secretion from the pancreatic beta cells.
<table>
<thead>
<tr>
<th>Product</th>
<th>Drug class</th>
<th>Available strengths (mg)</th>
<th>Labeled uses</th>
<th>Dose range, Adults</th>
<th>Dose titration, Adults</th>
<th>Generic available</th>
</tr>
</thead>
</table>
| Chlorpropamide          | First-generation sulfonylurea   | 100, 200                 | Management blood sugar in Type 2 diabetes mellitus as an adjunct to diet and exercise | Adult: 250 mg daily
Genetic: 100-125 mg daily
Renal impairment: avoid use in pts with CrCl <50. In Pts CrCl is >50 reduce by 50%
Hepatic impairment: reduced initial dose | Adult: at 5-7d increase 50-125 mg at 3-5 d intervals as needed
Genetic: see adult, may require slower up titration | Yes                             |
| Glimepiride/Amaryl®     | Second-generation sulfonylurea  | 1, 2, 4                  | Management of Type 2 diabetes mellitus as an adjunct to diet and exercise   | Adult: 1-2 mg daily
Genetic: 1 mg daily
Renal impairment: 1 mg daily
Hepatic impairment: no adjustment needed in minor. Severe impairment use is contraindicated | Adult: 1-2 mg every 1-2 weeks as needed
Genetic: conservative titration
Renal: conservative titration | Yes                             |
| Glipizide/Glucothrol®/Glucothrol® XL | Second-generation sulfonylurea | Immediate release, 5, 10 Extended release, 2, 5, 10 | Management of Type 2 diabetes mellitus as an adjunct to diet and exercise | Adult: 5 mg daily
Genetic: 2.5 mg daily
Renal impairment: No adjustment needed in labeling
Hepatic impairment: 2.5 mg daily | Adult: IR: 2.5-5 mg as frequently as every 7 days
Adult ER: adjustments no more frequently than every 7 days
Genetic: IR: 2.5-5 mg every 1-2 weeks as needed
Genetic: ER: Conservative titration | Yes                             |
| Glyburide/Diabeta®/Glynase® | Second-generation sulfonylurea | Tablet (mg): 1.25, 2.5, 5 Micronized tablet (mg): 1.25, 2.5, 5 | Adjunct to diet and exercise for the management of Type 2 diabetes | Adult: 2.5-5 mg daily
Adult Micro: 1.5-3 mg daily
Genetic: 1.25-2.5 mg daily
Renal impairment: not recommended in CrCl <50
Hepatic: avoid in severe disease | Adult: no more than 2.5 mg/day at weekly intervals
Adult Micro: no more than 1.5 mg/day at weekly intervals
Genetic: 1.25-2.5 mg every 1-3 weeks | Yes                             |
| Tolazamide/Tolinase®    | First-generation sulfonylurea   | 250, 500                 | Adjunct to diet for the management of mild-to-moderately severe, stable, Type 2 diabetes mellitus | Adult: FBG<200 100 mg daily
Adult FBG=200: 250 mg daily | Adult: FBG<200 100 mg/day at weekly intervals
Genetic: see adult
Renal impairment: Conservative initial treatment
Hepatic: Conservative initial treatment | Yes                             |
Pharmacokinetics:

Sulfonylureas are well absorbed after oral administration. Glipizide absorption is delayed by food. All sulfonylureas are highly bound to plasma protein (90% to 99%). Plasma protein binding is least for Chlorpropamide and greatest for glyburide. Sulfonylureas are metabolized in the liver and excreted in the urine.

<table>
<thead>
<tr>
<th>Product</th>
<th>Onset</th>
<th>Peak</th>
<th>T1/2 plasma</th>
<th>Metabolism</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpropamide</td>
<td>1h</td>
<td>Serum: 2-4h</td>
<td>36h</td>
<td>50-200h in ESRD</td>
<td>80% Hepatic, primary CYP2C9</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>2-3h</td>
<td>Serum: 2-3h</td>
<td>5-9h</td>
<td>Hepatic CYP2C9</td>
<td>M1 metabolite: 33% activity</td>
</tr>
<tr>
<td>Glipizide</td>
<td></td>
<td>Serum: IR1-3 h ER 6-12h</td>
<td>2-5h</td>
<td>Hepatic CYP2C9</td>
<td></td>
</tr>
<tr>
<td>Glyburide</td>
<td>15-60m</td>
<td>Serum: 2-4h</td>
<td>10h: 4h for micronized</td>
<td>Hepatic CYP2C9</td>
<td>Weak activity eliminated</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>20m</td>
<td>Serum: 3-4h</td>
<td>7h</td>
<td>Hepatic, exact mechanism</td>
<td>5 metabolites: activity 0-70%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>unknown</td>
<td></td>
</tr>
</tbody>
</table>

Key: IR = immediate release, ER = extended release, ESRD = end stage renal disease, N/A = information not available

ADR of Sulfonylurea: -

Hypoglycemia
Hypersensitivity reactions

Other adverse effects of sulfonylureas include nausea and vomiting, occasional hematologic reactions (especially leukopenia and thrombocytopenia, and hemolytic anemia in susceptible patients), cholestatic jaundice, and dermatologic effects. Sulfonylureas are teratogenic in animals (large doses). Patients taking sulfonylureas tend to gain weight, which is a problem in type 2 diabetics, who tend to be obese. Sulfonylureas have a disulfiram-like effect.

Glimepiride

Glimepiride is a newer, novel second generation Sulphonylurea. It increases insulin secretion by stimulating beta cells and also has significant extra pancreatic activity.

1. Beta Cell Action:

Glimepiride binds to a specific receptor site 65 KDS region in the beta cell while Glibenclamide binds to 140 KDs region. Glimepiride binds to its receptor 2.5 to 3 times faster and dissociates from it binding site 8 to 9 times greater than Glibenclamide.

The mechanism of insulin secretion and release is similar to Glibenclamide i.e. via the closure of ATP dependent potassium channel and opening up of voltage dependent calcium channel and increase of intracellular calcium concentration leading to exocytosis of insulin.

Sulphonylureas act at the level of potassium – ATP channel. However current Sulphonylureas may not stimulate beta cells in a controlled fashion or in proportion to the blood glucose level, because of their fixed blocking of potassium-ATP channel.

Agents that accomplish this in a more flexible fashion may lead to less secondary failure. Glimepiride which binds to a different portion of Sulphonylurea receptor, leading to less fixed blockage of potassium-ATP channel may have less secondary failure.

The amount of insulin secretion is more or equivalent to that of Glibenclamide but the secretion with glimepiride is very quick and lasts for a short time than Glibenclamide and hence there will be no hyperinsulinism and reduced likelihood of in-between meal hypoglycemia.

2. Insulin-independent blood glucose decreasing activity of Glimepiride: (Extra-pancreatication):

Glimepiride exhibits a more pronounced insulin independent blood glucose decreasing activity compared to glibenclamide. This can be explained by stimulation of glucose transport and nonoxidative glucose metabolism and adipose tissue and muscle cells.

The increased glucose transporter activity is brought out by increased translocation of GLUT-4 isoform from inside the cell to surface of adipocytes and muscle.

It increases insulin sensitivity and decreases insulin resistance. If hyperinsulinemia is a concern in therapy of Type 2 diabetes, the higher insulin-independent blood glucose decreasing activity of glimepiride might be of therapeutic relevance.
Thus the more pronounced blood glucose decreasing activity of glimepiride is brought out by its quick insulin release in conjunction with an insulinindependent glucose decreasing activity at the periphery. The extra pancreatic effects of glimepiride may explain the lesser degree of insulin stimulation for a given fall in blood glucose, in both short term and longer clinical studies compared with other sulphonylureas.

In vitro, glimepiride stimulates glycogen formation, glucose transport and other insulin like effect. It decreases hepatic gluconeogenesis.

There is not much difference in absorption whether glimepiride is given just before or along with food. The peak concentration of the drug is attained in one hour. The half life of the drug is 9 hours. The drug is 100% bioavailable. It has dual mode of excretion 40% through liver and 60% through kidney. The metabolites are not much active.

The quick insulin release, increased peripheral tissue glucose disposal and the peak action at one hour are responsible for smooth control of postprandial hyperglycaemia.

The prolonged half life suggests that once daily dosing of glimepiride is enough to maintain blood glucose control for 24 hours.

Efficacy wise glimepiride is equivalent to that of glibenclamide. It decreases both fasting and post prandial hyperglycaemia.

The HbA1c decreases 1 to 2% within three months with 1 to 2 mg dose. The fall in HbA1c is upto 3.5% when the drug is initiated in diabetics with HbA1c more than 10.5%. There is no increase in fasting C – peptide and insulin levels even upto one year of treatment.

The hypoglycaemic episodes are very few in number, lesser in intensity and are of shorter duration. The hypoglycaemic episodes vary from 0.9 to 1.7% when compared to glipizide and glibenclamide, both of which cause more severe hypoglycaemic episodes.

Glimepiride safeguards the physiological suppression of endogenous insulin release during active physical exercise, implying that post exercise induced hypoglycaemia may not occur with the drug.

It has been observed in animal studies that platelet inhibitory effect of glimepiride is much more pronounced than gliclazide and hence it may have a preventive effect in the development of microvascular complications.

**Dosage and Administration:**

Glimepiride is indicated in Type 2 diabetics when diet and exercise fails. Dosage is individualised for each patient so as to achieve and maintain satisfactory blood glucose level at a minimum effective dose.

He fasting blood glucose andHbA1c measurements should be performed periodically.

The usual starting dose of glimepiride is 1 mg.

Maximum initial dose 2 mg once daily taken just before breakfast or with the first main meal of the day. Further increments can be made at 1 or 2 week intervals in increments of 2 mg.

The patient’s blood glucose response should guide dosage titration. The usual maintenance dose is 1 to 4 mg once daily.

Maximum recommended dose is 8 mg once daily. There is no need to split the dosage to twice daily.

Once daily dosage will improve patient’s compliance.

**Combination Therapy with Insulin :**

For patients with secondary failure to other sulphonylureas when glimepiride and insulin therapy is indicated, the recommended dosage of glimepiride is 8mg once daily. Insulin is then titrated from a low dosage upward with approximately once-weekly dose increase guided by fasting blood sugar measurements. Glimepiride lowers daily insulin dosage requirements.

**In Special Populations :**

In American clinical trials, tight control i.e. HBA1c levels of 7.2% or lower was achieved in 68% of obese diabetics and in 78% of diabetics with hypertension.

No marked difference in the safety profile and daily dosage were observed between patients who were young and elderly, obese and non-obese, male and female and among patients of various racial phenotypes.

Glimepiride has less effect on cardiovascular system than do glyburide and glipizide and has decreased binding to cardiovascular ATP dependent potassium channel causing one-third the degree of inhibition seen with glyburide.

There is also less alteration of coronary blood flow. Thus interestingly, glimepiride appears to be "Pancreas Specific" in its effect on the potassium-ATP channel and hence it could be used in cardiac patients with mild to moderate hyperglycemia.

Glimepiride should not be used in pregnancy and in lactating mothers.

No clinically significant drug interactions were observed with commonly used drugs such as calcium channel blockers, ACE inhibitors, H1 receptors antagonists, fibrates, NSAID, sympathomimetic agents, sulphonamides and thyroid hormones.

Clinical studies indicate that glimepiride offers significant benefits in the management of Type 2 diabetics.

1. It has the greatest (mgm. for mgm.) glucose lowering effect when compared to other sulphonylureas.

2. It achieves tight control in more than two thirds of the patients.

3. It maintains effective control upto 2 1/2 years.
4. It reduces insulin resistance and has a unique beta cell receptor binding capability.
5. Once daily dosage will improve patients compliance.
6. It has insulin sparing activity. Glucose levels are controlled without meaningful increase in fasting insulin and in Type 2 diabetics requiring exogenous insulin, glimepiride lowers daily insulin dosage requirements.

**Meglitinides**: 

Meglitinides or glinides are a class of drugs used to treat type 2 diabetes.

In the late 1970s, a compound was developed by the addition of a COOH group to the non-sulfonylurea end of the Glibenclamide molecule (later called Meglitinide). It was shown to be hypoglycemic action through blockade of K<sub>ATP</sub> channel and augmentation of insulin secretion Henquin (1990). Unlike the sulfonylurea drug Glibenclamide, it has similar binding affinity for the different sulfonylurea receptors SUR1 (the predominant form in the pancreatic islet beta-cell and neurons), SUR2A (the predominant form in heart and skeletal muscle), and SUR2B (the predominant form in smooth muscle) Meyer et al (1999).

**Mechanism of Action:**

They bind to an ATP-dependent K<sup>+</sup> (K<sub>ATP</sub>) channel on the cell membrane of pancreatic beta cells in a similar manner to sulfonylureas but have a weaker binding affinity and faster dissociation from the SUR1 binding site. This increases the concentration of intracellular potassium, which causes the electric potential toward the intracellular side of the membrane to become more positive. This depolarization opens voltage-gated Ca<sup>2+</sup> channels. The rise in intracellular calcium leads to increased fusion of insulin granula in the cell membrane, and therefore increased secretion of (pro) insulin.

**Repaglinide--- Prandial Glucose Regulator**

Repaglinide is a non-sulphonylurea antidiabetic agent and a short acting insulin secretagogue.

It is a benzoic acid derivative and is an analog of meglitidine family.

The meglitidine shares the non-sulphonylurea moiety of glibenclamide.

**Mode of action:**

Repaglinide has a unique binding site on beta cell, different from that of glibenclamide. It acts via closure of ATP dependent K channel in beta cell. It to 3 to 5 times more potent insulin releaser than glibenclamide but its action is short lived.

The half life of the drug is 2.5 hours and peak action is less than one hour. It reduces post-prandial blood sugar by 4 to 6 mmol and HbA<sub>1c</sub> by 2%. It is metabolized in the liver and secreted in bile.

**Repaglinide vs Glibenclamide:**

When compared to glibenclamide, Repaglinide has the following characteristic feature:

1. Fast Absorption
2. Short biological half life
3. Short duration of insulinotrophic activity
4. Lowest post-prandial Blood glucose
5. No in-between meal hypoglycaemia or hyperinsulinemia.

**Uses :**

a) **Primary Therapy in Type 2 Diabetes**

Repaglinide is a prandial glucose regulator. It has a fast onset and short duration of action. The initial dose is 0.5 to 1 mg and gradually increased upto 2 to 4 mg. It should be administered three times a day just, before along or immediately after a meal and offers greater flexibility in meal times and drug dosing.

b) **Useful in patients who eat at irregular times or miss a meal:**

Repaglinide increases insulin secretion sufficient to control the post meal surge and not for so long as to produce hypoglycaemia in-between meals and especially when a meal is missed or delayed as is the case with long acting insulinotrophic agents. So, there is no in-between meal hypoglycaemia

1. The intermittent stimulation of K channel that prevents down-regulation of receptors and consequent refractoriness and secondary failure of therapy.
2. It has no effect on ATP-regulated K channel of cardiocytes or vascular smooth muscle cells (Landry D. L. Oliver, Jan. 1992) and therefore may be preferable to compounds that produce this effect.
3. Rapid non-renal inactivation and elimination results in a short swift, "Antihyperglycaemia" action. So, it can be administered safely in patients with compromised early renal or hepatic function.

**Combination Therapy : Regaplinide and Metformin:**

Regaplinide acts only at beta cells leading to insulin release, whereas metformin bypasses beta cell and acts at periphery, liver, muscle and adipose tissue.

The actions are complementary to one another, when both the drugs are combined. The fall in HbA1c is significant within three months in most Type 2 diabetics.

**Dipeptidyl peptidase-4 inhibitors:**

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a group of antihyperglycemic medications used to manage type 2 diabetes mellitus. DPP-4 inhibitors, known as gliptins, approved by the Food and Drug Administration (FDA). Apart from antihyperglycemic effects, this class of drugs possesses antihypertensive effects, anti-inflammatory effects, antiapoptotic effects, and immunomodulatory effects on the heart, kidneys, and blood vessels independent of the incretin pathway.

**Mechanism of Action:**

DPP-4 is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion.

GLP-1 is a hormone secreted by enter endocrine L cells of the small intestine, which lowers blood glucose by stimulating insulin secretion, reducing glucagon concentrations, and delaying gastric emptying.

**Administration**

All the DPP-4 inhibitors are administered orally, once daily, before or after meals. A study of oral and intravenous administration of Sitagliptin in healthy individuals demonstrated an 87% oral bioavailability.

**Adverse Effects**

Gliptins are associated with a low incidence of adverse events, including hypoglycemia, and have weight-neutral effects. However, the risk of hypoglycemia increases when used in conjunction with sulfonylureas. The most common side effects noticed with the DPP-4 inhibitors Sitagliptin and Saxagliptin are upper respiratory tract infection (URTI), nasopharyngitis, headache, urinary tract infection, arthralgia.

**Biguanide:**

The biguanides are derivatives of the compound biguanide (guanylguanidine) that exert a blood glucose-lowering effect in type 2 (non-insulin dependent) diabetes mellitus. The main biguanides are metformin (dimethylbiguanide)
and phenformin (phenethylbiguanide), which were described in 1957 and buformin (butylbiguanide), which was described in 1958 (Schafer, 1983, Bailey, 1992). Phenformin and buformin were withdrawn from clinical use in most countries in the late 1970s due to a high incidence of associated lactic acidosis. Metformin, which has a much lower risk of lactic acidosis, is used widely in the treatment of type 2 diabetes.

**Mechanism of Action:**

All biguanides display an inhibitory effect on complex I and inhibit the rate of oxygen consumption, thereby causing energy stress, increase in AMP/ATP ratio, and activation of AMP Kinase (AMPK).

**ADR:**

The most common side effect is diarrhea and dyspepsia, occurring in up to 30% of patients. The most important and serious side effect is lactic acidosis, therefore metformin is contraindicated in advanced chronic kidney disease. Kidney function should be assessed before starting metformin. Phenformin and buformin are more prone to cause acidosis than metformin.

**Thiazolidinedione:**

The use of thiazolidinediones, also called "glitazones," in managing type 2 diabetes can help with glycemic control and insulin resistance. There are two thiazolidinediones, rosiglitazone, and pioglitazone, currently approved by the FDA as monotherapy or combined with metformin or sulfonylureas to manage type 2 diabetes mellitus. These medications should be in conjunction with lifestyle modifications such as diet, exercise, and weight reduction. Thiazolidinediones may also be used to treat polycystic ovarian syndrome, as these may lead to improved endothelial function, improved ovulation, and reduction of insulin resistance.
Thiazolidinediones (TZDs) are taken orally once daily, with or without food. Before initiating treatment and periodically during therapy, LFTs and HbA1C levels require monitoring.

**Mechanism:**

The thiazolidinediones increase insulin sensitivity by acting on adipose, muscle, and, to a lesser extent, liver to increase glucose utilization and decrease glucose production. TZDs function by regulating gene expression through binding to peroxisome proliferator-activated receptor-gamma (PPAR-gamma), a nuclear transcription regulator.

**ADR:**

There are several undesirable side effects to thiazolidinedione’s, particularly with long-term use. **Edema and Congestive Heart Failure:**

TZDs have been shown to cause dose-related fluid retention in up to 20% of patients. Methods of fluid retention include PPAR-gamma receptors in the distal nephron and insulin-activated epithelial sodium channels in the collecting tubules. PPAR-gamma activation stimulates sodium reabsorption, acting at the same site as aldosterone. Patients with preexisting edema or concomitant insulin therapy are at higher risk of edema and should start on the lowest available dose.

**Weight Gain:**

Adipocytes have the highest concentration of PPAR-gamma receptors in the body. The mechanism behind the weight gain is due to a combination of factors. TZDs up regulate PPAR-gamma receptors in the central nervous system, leading to increased feeding. TZD agents expand adipose tissue mass via the maturation of preadipocytes into mature adipocytes and increase fat storage by increasing free fatty acid movement into cells. Additionally, fluid retention can increase weight.

**Fractures:**

Several studies have demonstrated an increased fracture risk and decreased bone density in patients taking TZDs compared to those taking insulin or other oral agents such as sulfonylureas. Proposed mechanisms for this
include PPAR-gamma activation and insulin-like growth factor down-regulation, which diverts the differentiation of osteoblasts into adipocytes and leads to bone loss.

**Bladder Cancer:**

Pioglitazone has, in some studies, shown correlations with an increased risk of bladder cancer. This effect varies in a duration-dependent and dose-dependent fashion. Also, most recent analyses do not support an increased risk. In contrast, rosiglitazone was not associated with an increased risk of bladder cancer in any analysis, suggesting the risk is drug-specific and not a class effect.

**Hepatotoxicity:**

Troglitazone, the original PPAR-gamma activator, was removed from the market primarily due to hepatotoxicity.

**Diabetic Macular Edema:**

Combination TZD and insulin therapy have correlated with an increased incidence of diabetic macular edema at 1-year and 10-year follow-up.

**Increased Ovulation and Teratogenic Effects:**

Patients with polycystic ovarian syndrome have shown an increased ovulation rate when using TZD and other insulin sensitizers.

**Alpha-Glucosidase inhibitors**

In human salivary amylase, pancreatic amylase and alpha-glucosidase are the enzymes involved in the digestion of starch. All complex carbohydrates like starch and sucrose have to be converted to simple carbohydrates in the small intestine by an enzyme alpha-glucosidase before absorption.

Drugs which inhibit the action of alpha-glucosidase known as glucosidase inhibitor, preventing the breakdown of complex carbohydrates thereby delay or preventing carbohydrate absorption. Glucosidase inhibitors are three types:

1. Reversible competitive inhibitors of alphaglucosidase. eg: a. Acarbose; b. Meglital
2. Irreversible glucosidase inhibitor eg: Gasternospermine.

Acarbose is freely available for clinical use. Other drugs are under clinical trial.

**Acarbose**

Acarbose is a psuedotetrasaccharide and is a reversible competitive inhibitor of the brush border alpha-glucosidases (mainly glucoamylase, sucrose and maltose) as well as alpha amylase. Acarbose binds to alpha-glucosidase with high affinity.

**Mode of Action:**

1. Acarbose blocks the digestion of starch, sucrose and maltose. The digestion of carbohydrate is delayed and occurs throughout the small intestine, rather than upper part of jejunum.

Absorption of glucose and other monosaccharides in not affected. The net result is a decrease in post prandial rise in blood glucose.

Most of the carbohydrate is eventually absorbed and that which is now absorbed is metabolised by the bacteria in the colon to short chain fatty acids which are then absorbed in the colon.

2. Acarbose decreases meal stimulated secretion of gastric inhibitory polypeptide and other gastrointestinal peptide (inhibitors) hormones.

There is smaller increase in post prandial blood sugar level that leads to smaller increase in insulin level.

3. Acarbose does not cause weight gain with the therapeutic doses.

**Side Effects:**

Abdominal fullness, borborygmi, increased intestinal flatulence and diarrhoea are major side effects of alpha-glucosidase inhibitors.

These side effects are due to undigested sugars passing through large bowel where bacterial fermentation occurs, producing both carbondioxide and large quantities of osmotically active glucose load, leading to diarrhoea and flatulence.

These symptoms occur in the first few weeks of treatment and abate with continued long term treatment.

**Degradation of Acarbose:**

Mostly occurs in the intestine. Some of the degradation products and the trivial amount of the parent drug enter systemic circulation and are excreted in urine.
Contraindications to Acarbose use are primary therapy for Type 1 diabetes, significant gastrointestinal disorders and pregnancy or lactation. Acarbose is administered orally three times a day and chewed with the first mouthful of food. Initial dose is 50 mg. Three times a day.

Uses:
In non-diabetics and in Type 2 diabetics acarbose produces a dose related decrease in post-prandial hyperglycemia. Acarbose therapy causes a corresponding reduction in post prandial plasma insulin response.
Long term treatment either as mono-therapy or in combination with S.U, acarbose improves basal blood sugar concentration as well. Thus insulin resistance decreases and sensitivity improves consequent to reduction in hyper-glycaemia.

5. In IDDM:
Long term treatment with acarbose reduces both post prandial and basal hyper glycaemia and reduces insulin requirement by 10 to 30 % interestingly, episodes of hypo-glycaemia between meals may be less frequent and less severe in IDDM.
In treatment of hypoglycemia in patients taking acarbose, only oral or IV (glucose) should be given. Sucrose and other complex carbohydrates should not be used.

Insulin sensitizers
 Sulphonylurea increase insulin secretion and may improve insulin sensitivity while the biguanide metformin improves insulin action.
One of the exciting areas in the management of Type 2 diabetes is the development of pathogenetically targetted drugs to overcome insulin resistance, namely the thiozolidinediones. They work mainly by reducing peripheral insulin resistance in adipocytes, skeletal muscles and to a lesser extent by decreasing hepatic glucose production. These drugs facilitate insulin action in liver, muscles and adipose tissue. They do not stimulate insulin secretion. Pioglitazone, englitazone and troglitazone are the thiozolidine derivatives.

Only Troglitazone is in clinical use. Troglitazone was developed in 1980 and was synthesized later with an alpha-tocopheral substitution and has antioxidant properties in addition to improving insulin sensitivity.

Mechanism of Action of Troglitazone:

In Adipose Tissue:
1. Thiozolidinediones increase glucose oxidation, lipogenesis and increase the expression of GLUT-4, the glucose transporters in adipose tissues.
2. Recently these drugs are found to interact or bind with the PPAR-Y (Peroxidase Proliferator Activated receptor –Y) nuclear receptor of adipocytes. PPAR – Y is the binding site for troglitazone and this leads to differentiation of insulin resistant large size adipocytes, into insulin sensitive small adipocytes, without increasing adipocyte mass and thereby reducing insulin resistance and improving insulin sensitivity.

Other suggested mechanism of actions are:
 a. by reducing white adipose tissue mass and increasing brown adipose tissue mass,
b. by decreased production of TNF alpha, leptin, and FFA levels in adipose tissue, all of which cause insulin resistance.

3. In Muscle:
Troglitazone [1] increases GLUT-4 and increases the activity of glycogen synthase. There is increased glyocogenesis and glycolysis.

4. In Liver:
Thiozolidinediones reduce hepatic glucose production by suppressing neoglucogenesis. This is by restoring the ability of insulin to suppress the expression in the liver of PEPK (phosphoenolpyruvate carboxykinase) the rate limiting enzymes of gluconeogenesis.

5. Thiozolidinediones have been suggested to decrease hyperglycaemia in activating protoinkinase which reduces kinase activity of insulin receptor.

6. Troglitazone reduces triglyceride level and NEFA. It also decreases cholesterol, increases HDL and to a lesser extent increases LDL level.

7. Troglitazone has no effect on body weight.

Safety data and Adverse Events:
Were reported from 30 clinical trials and 74000 weekly patient exposur to Troglitazone.
 a. No hypoglycaemia occurs with Troglitazone when used alone.
b. 2 to 3 % reduction in haemoglobin level with 5 to 7% elevation in plasma volume have been reported. Hb% level did not fall outside the normal range.
c. Liver Enzyme Activity increased to more than 3 fold of normal in some patients on Troglitazone treatment. Varying degrees of liver damage have been received by US, FDA. This include irreversible damage and death in one. This is probably an idiosyncratic reaction.
Prescribing Information

Troglitazone is metabolised by the liver and excreted into the bile. The presence of renal insufficiency does not affect the serum level or metabolism of the drug.

1. In Type 2 diabetics, this is accompanied by concomitant reduction in both fasting and post prandial insulin levels. There will be significant reduction in triglyceride level and an increase in HDL cholesterol level. Dosage is 200-600 mg/day average dosage is 400 mg/day. Dosage is once per day with breakfast and titration is not necessary. Troglitazone may be started either as monotherohy or in combination with sulphonylureas, acarbose, metformin and with insulin.

2. In poorly controlled Type 2 diabetics on insulin therapy, the insulin dosage reduction is not recommended at the outset. Along with insulin, troglitazone therapy is started. Once fasting blood sugar falls to 120-140 mg a reduction of 10 to 20% of insulin dose is recommended in order to avoid hypoglycaemia. Some studies have reported (I) a reduction of insulin dosage up to 58%, (ii) reduction of insulin injection from three to one per day in 40% of diabetics treated with Troglitazone and (iii) discontinuation of insulin in 10% of diabetics.

3. Troglitazone is the ideal drug for syndrome X and other insulin resistant states.

4. In IGT:
   In patients with IGT, Troglitazone decreases insulin resistance and improves insulin sensitivity. It reduces insulin level and normalises blood glucose level and prevents or postpones onset of Type 2 DM.

5. In Women with Polycystic Ovary Syndrome
   
   with IGT:
   Troglitazone improves glucose tolerance, insulin sensitivity and causes a fall in androgen level Plasaminogen activator inhibitor – 1 (PAI-1) level also falls (a prothrombotic factor).
   
   Advantages of Troglitazone:
   1. Once a day dosage
   2. No dosage titration
   3. No hypoglycaemia when used alone
   4. No weight gain
   5. Can be used along with sulphonylurea, Metformin and Insulin.
   
   Hidden Benefits of Troglitazone:
   1. Decrease in systolic, diastolic and mean blood pressure.
   2. Decrease in triglyceride level. This means (1+2) indirectly a reduction in anti-hypertensive and triglyceride lowering drugs.
   3. Decreases PAI-1 level, a prothrombotic factor.
   4. May prevent or delay beta cell exhaustion.

Insulin Secretagogues

Beta Cell Secretory defect, namely the insulin deficiency is an important factor in the pathogenesis of Type 2 diabetes, particularly during later stages of the disease.

As the disease progresses, there is:
1. Loss of sensitivity of insulin secretion to a rise in blood glucose concentration and
2. Impaired processing of pro-insulin.

Insulin secretagogues provide useful therapeutic approaches if used early in the natural history of the disease. An ideal insulin secretagogue would restore beta cell sensitivity to glucose and at the same time ensure adequate biosynthesis, processing and secretion of insulin to other nutrients, hormones and neural factors.

Insulin secretagogues can be divided into
(i) Initiators of Insulin secretion eg. Glimepiride and Repaglinide;
(ii) Potentiator of insulin secretion eg. GIP and GLP –1 (Gastric Inhibitory polypeptide, Glucagon Like Peptide).
Reference:

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