

**Education-Family Physician Corner**

**Therapeutic Choices within Diabetes**

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The field of diabetes has experienced various evolutionary leaps in different aspects of care. Lifestyle modifications are considered the mainstay of therapy for diabetic patients, it is estimated that 80% of patients with Type II diabetes are treated pharmacologically<sup>1</sup>.

Successful research and development efforts have yielded new agents and new classes of drugs that are now available for the treatment of diabetes mellitus. The following are the list of key aspects in anti-diabetic medication.

**Insulins**

**A) Mechanism of Action:** Insulin was discovered in 1920. It is a peptide hormone delivered parenterally<sup>2</sup>. Many attempts were made to provide other modes of delivery but the subcutaneous one is still the method of choice. Recently, insulin was produced by DNA recombinant technology. Various types of insulin were produced with variable absorption rate and duration of action. Insulin produced in two main forms, the long acting or basal and the short acting or prandial form. A mixture of both does exist. The new insulin analogues provide many advantages over the conventional insulins including flatter and faster response and thus lesser hypoglycemia<sup>3</sup>.

**B) Key Trial Data and Long-term Outcome Studies of the Class**

**Type I:** The Diabetes Control and Complications Trial (DCCT) showed that retinopathy, neuropathy and nephropathy were decreased in Type I diabetics who had tighter glycemic control<sup>4</sup>.

A follow-up study to the DCCT which is the Epidemiology of Diabetes Interventions and Complications (EDIC) showed that the tight glycemic control yielded 42% reduction (p=0.02) in the risk of any cardiovascular event and 57% reduction (p=0.02) in non-fatal myocardial infarction, stroke or cardiovascular death during the initial period of the study<sup>4</sup>. Adjustment for confounding risk factors, such as, microalbuminuria and dyslipidemia did not eliminate the cardioprotective effect of tight glycemic control. The term 'legacy' then appeared which refers to the continuous cardiovascular benefit of intensive glycemic control in the early history of the disease<sup>4</sup>.

**Type II:** The United Kingdom Prospective Diabetes Study (UKPDS) proved that tight glycemic control with either insulin or sulfonylureas in newly diagnosed Type II diabetic

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patients resulted in microvascular risk reduction<sup>5</sup>. A follow-up study to the UKPDS showed persistent cardioprotective and reductions in total mortality, diabetes-related deaths and myocardial infarction<sup>5</sup>.

**C) Side Effects and Safety:** Hypoglycemia is the major side effect of insulin. Usually, it is iatrogenic with aim to achieve tighter glycemic control. The UKPDS and DCCT have quoted major hypoglycemia in 1.8% and 3.9% respectively<sup>4,5</sup>. Newer insulin analogues are associated with less hypoglycemia and better glycemic control<sup>4,5</sup>.

No consistent relationship was seen between insulin therapy and cancer occurrence<sup>6</sup>. Weight gain associated with insulin therapy is well documented and means about 3-5 kg<sup>5</sup>.

### **GLP-1 Agonists (Glucagon-like Peptide-1)**

**A) Mechanism of Action:** The incretin effect is a physiological mechanism through which the GI tract produces markers during meal ingestion to augment nutrient-induced insulin secretion. This in turn reduces the food related excursion of blood glucose. The incretin effect is mediated through GLP-1 and GIP (gastric inhibitory peptide)<sup>1,2</sup>.

**B) Key Trial Data:** In placebo-controlled, randomized trials, both exenatide and Liraglutide reduce glycosylated hemoglobin (HbA1c) by about 1% when used in combination with metformin and/or sulfonylureas and in combination with metformin and a thiazolidinedione for Liraglutide<sup>7</sup>.

The Liraglutide Effect and Action in Diabetes (LEAD) trial demonstrated 3.6 mmHg to 6.7 mmHg reductions in systolic blood pressure in the Liraglutide-treated group compared with those treated with other agents or placebo. The cardioprotective effect may be attributed to decrease in CRP or improve in cardiac perfusion<sup>7,8</sup>.

**C) Side Effects:** The main side effect is GI disturbance that wanes off within 2 to 6 weeks<sup>7,8</sup>.

### **Biguanides**

**A) Mechanism of Action:** Biguanides increases insulin sensitivity, mainly in liver and skeletal muscle. It decreases glucose production through suppression of hepatic gluconeogenesis and increases peripheral glucose consumption. The cardioprotective effect of Biguanides could not be totally attributed to its blood glucose-lowering effect but may be explained by modulating the increase in circulating markers of endothelial function, fibrinolysis and chronic inflammation<sup>9</sup>.

**B) Key Trial Data:** In the UKPDS, Metformin reduced any diabetes-related endpoint (p=0.0034), all-cause mortality (p=0.021) and stroke (p=0.032)<sup>5</sup>.

**C) Side Effects:** Gastrointestinal upset is the most frequent complaint but the most worrying side effect is lactic acidosis especially in those patients with renal and cardiac failure. The risk of lactic acidosis associated with metformin is rare, it is estimated to be one to five cases per 100,000<sup>5,9</sup>.

**D) Long-term Outcome Studies of the Class:** The UKPDS post-trial monitoring results demonstrated maintenance of the relative risk reductions for any diabetes-related end point (21%), myocardial infarction (33%) and all-cause mortality (27%); this continued benefit is termed as 'Legacy Effect'<sup>5,9,10</sup>.

## Sulfonylureas

**A) Mechanism of Action:** Sulfonylureas are considered insulin secretagogue which involves a direct secretory effect on the pancreatic islet beta-cells. The sulfonylureas act by binding to the transmembrane sulfonylureas receptor (SUR-1) on beta cells of the pancreas which leads to the closing of the potassium-sensitive ATP channels on the cell membrane. This in turn results in the reduction of intracellular potassium and thus membrane depolarization takes place. This is followed by increased calcium influx which in turn promotes the release of preformed insulin granules adjacent to the plasma membrane<sup>1,2,11</sup>.

**B) Key Trial Data:** The UKPDS trial examined the efficacy of sulfonylureas in reducing HbA1c in comparison with either insulin or diet alone in almost 4000 newly diagnosed Type II diabetes patients. After three years of the trial, the HbA1c values in the sulfonylureas-treated patients in comparison to insulin and diet groups were 6.85%, 7% and 7.6%, respectively (p<0.001)<sup>5</sup>.

**C) Side Effects:** The most common and alarming side effect of sulfonylureas is hypoglycaemia. Longer-acting sulfonylureas, such as, glibenclamide or modified-release gliclazide impose greater risk for more severe and prolonged hypoglycaemia. Another undesirable effect of sulfonylureas is weight gain, especially in obese patients. This may be attributable to the fact that this class of drugs increase insulin secretion and decrease glucose loss in the urine. On average, patients gain roughly 1-4 kg<sup>1,2,11</sup>.

**D) Long-term Outcome Studies of the Class:** The famous UKPDS trial has shown that after 10 years of intensive therapy with sulfonylureas or insulin, the decrease in HbA1c was significantly (p<0.001) higher in the intensive group compared to the conventional group<sup>5</sup>. Similarly, the reduction in any diabetes related complications was significantly (p=0.029) higher in the intensive group. This risk reduction was mainly attributed to the reduction in the risk of microvascular end points (renal failure, death from renal failure, retinal photocoagulation or vitreous hemorrhage) (p=0.0099)<sup>5,7,11</sup>.

In the UKPDS post-trial follow-up, 3277 patients were followed for six years. After one year of follow-up, those intensively treated (taking sulfonylureas or insulin during the trial) had a significant reduction in any cause mortality (odds ratio 13%, p=0.007), and in myocardial infarction (odds ratio 15%, p=0.01)<sup>5,11</sup>.

Recently, specific concern in cardiology patients was raised regarding the class relation to ischaemic preconditioning and percutaneous intervention, but evidence by randomized-controlled trial data is lacking regarding this context<sup>5,11</sup>.

## Glinides (Meglitinides)

**A) Mechanism of Action:** Though structurally unrelated to sulfonylureas; this class exerts their hypoglycemic activity by closing adenosine triphosphate (ATP)-sensitive potassium channels (sulfonylurea receptor, SUR1/KIR 6.2) in the  $\beta$ -islet cells of the pancreas.

These agents, unlike sulfonylureas, have a much more rapid onset and shorter duration of action mimicking endogenous insulin<sup>1,2,12</sup>.

**B) Key Trial Data:** Few clinical studies are undertaken on this class. In 40 Type II patients administration of mitiglinide significantly increased plasma insulin levels at 120 minutes postprandial, compared to placebo, ( $p < 0.001$ ). Plasma glucose levels at 120 minutes were significantly lower in the mitiglinide group ( $p < 0.001$ ), long term trials are deficient in this class<sup>1,2,12</sup>.

**C) Side Effects:** The most common adverse effects in Phase 2 and Phase 3 studies have been hypoglycemia. Weight gain and peripheral edema were no more common in patients using the combination of mitiglinide and pioglitazone than in patients receiving pioglitazone alone<sup>1,2,12</sup>.

### Thiazolidinediones

**A) Mechanism of Action:** Thiazolidinediones (TZD) increase insulin sensitivity. It is a ligand for the nuclear hormone receptor PPAR $\gamma$ , which binds and modulates its transcriptional activity. PPAR $\gamma$  is present mainly in adipose tissue, but it is also found in pancreatic beta cells, muscle and liver. TZDs facilitate glucose uptake by increasing transcription of GLUT-4 glucose transporters<sup>1,2,13</sup>.

**B) Key Trial Data:** TZDs as monotherapy or in combination are effective in improving glycemic control and lowering glycosylated hemoglobin (HbA1c) by between 0.65% and 1.26%. A Diabetes Outcome Progression Trial (ADOPT) compared the efficacy of glycemic control in Type II diabetes patients receiving monotherapy with a TZD (rosiglitazone), metformin or sulfonylureas. In the monotherapy, there was 32% risk reduction of failure with rosiglitazone compared with metformin and 63% risk reduction of failure with rosiglitazone versus sulphonylureas<sup>1,2,13</sup>.

**C) Side Effects and Safety:** A meta-analysis published in 2007 caused the withdrawal of rosiglitazones as it showed an increased risk of cardiovascular morbidity and mortality by 40% and 60% respectively<sup>13</sup>.

The difference between pioglitazone and rosiglitazones cardiovascular effect may be attributed to difference in lipid effect.

Weight gain associated with TZDs was attributed to several factors including redistribution of fat, fluid retention and increased leptin. Studies have shown 1-2 kg weight increase<sup>13,14</sup>. The incidence of pedal edema ranged from 3% to 5%<sup>13,14</sup>. Heart failure associated with TZDs is attributed mainly to fluid retention and weakened myocardium<sup>13,14</sup>.

### Gliptins (DPP-4 Inhibitors)

**A) Mechanism of Action:** Gliptins act through inhibition of DPP-4 as incretin enhancers. DPP-4 inhibitors inhibit the breakdown of native GLP-1, increasing its concentration and the physiological effect of GLP-1 on glucose-stimulated insulin release. The first Gliptin released is Sitigliptin, it was introduced in 2007<sup>15</sup>. Gliptins are considered an add-on therapy. Gliptin acts in response to glucose presence unlike sulfonylureas which act regardless of glucose excursions<sup>15</sup>.

**B) Key Trial Data:** In a comparative study of sitagliptin and metformin against glipizide (titrated up to 20 mg), maintained a comparative reduction in HbA1c<sup>16</sup>. In this study, 4.9% of sitagliptin patients reported hypoglycaemia events compared with 32% of glipizide patients suggesting that the counter-regulatory response of glucagon was not compromised at low glucose concentrations. Also, sitagliptin tended to lower body weight compared to glipizide<sup>16</sup>.

**C) Side Effects:** Post marketing long-term safety of the gliptins is still awaited. Some reported cases of acute pancreatitis, which have been associated with the use of sitagliptin and vildagliptin, but this was not confirmed by clinical trials<sup>15-17</sup>. Others reported adverse immune response in the form of higher infection rates in patients using gliptin. The long-term safety of gliptins in patients with liver disease is under scrutiny<sup>15-17</sup>.

**D) Long-term Outcome Studies of the Class:** As pointed before, the long-term safety of this class is still awaited and its effect in reducing the incidence of diabetes morbidity and mortality is yet to be established.

### **$\alpha$ -Glucosidase Inhibitors**

**A) Mechanism of Action:** The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucoside hydrolase enzymes. This leads to delayed postprandial absorption of glucose and thus decreases post prandial hyperglycemia. Acarbose is rarely used as monotherapy. It is usually used as add-on therapy to sulfonylureas, insulin or metformin<sup>1,18</sup>.

**B) Key Trial Data:** The United Kingdom Prospective Diabetes Study (UKPDS 44) compared acarbose or a matching placebo<sup>5,18</sup>. Acarbose appeared to be equally effective as monotherapy or with oral antidiabetic agents or insulin or their combination, producing an improvement of 0.5% in HbA1c. The duration of this study was not long enough to comment on any possible reduction in diabetic complications<sup>5,18</sup>.

**C) Side Effects:** Flatulence and GI disturbance are the main side effects of this class. Only 39% of subjects remained on acarbose, compared with 58% of subjects on placebo in the UKPDS 44<sup>5,18</sup>.

### **Amylin Analogues**

**A) Mechanism of Action:** Amylin is a peptide hormone that is co-secreted with insulin and shares the same processing enzymes from the pancreatic  $\beta$ -cell and is thus deficient in diabetic people. It primarily acts by reducing post prandial glucose concentration which is a main cardiovascular risk. Amylin agonists display some of the beneficial effects of GLP-1<sup>19</sup>.

**B) Key Trial Data:** Short term trials of less than 4 weeks in Type I and Type II patients have demonstrated a significant reduction in serum fructosaminase and PPG using infusion of Amylin analogues (PRAMLINTIDE) postprandial. No evidence of increased insulin sensitivity both in peripheral tissues and in the liver<sup>19</sup>.

Several large scales phase III studies have shown promising A1C reduction of 0.4-0.6% especially during the first 13 weeks of QID use of Pramlintide as an adjunctive therapy in both Type I and Type II patients<sup>19</sup>.

C) **Side Effects:** The main side effects as anticipated would be GI effects and augmentation of insulin-mediated hypoglycaemia<sup>19</sup>.

Table 1 shows that the previous data that compares the different ideal drug parameters<sup>20,21</sup>.

**Table 1: Comparison of Anti-diabetes Classes**

Parameters	Insulin	Big	Sulph	Gliptins	Glinides	GLP	TZD	Acarbose	Amylin
Hypoglycemia	+	-	++	-	+	-	-	+	+/-
β-cell mass	NA	-	-	+	-	+	+/-	-	-
Weight increase	++	-	++	-	+	-	++	-	+/-
Micro & macro	++	++	+/-	?	?	?	--	?	?
Carcinogenic	+/-	-	-	?	?	?	+/-	?	?
Plausibility	+	+/-	+	+	-	-	+	-	?
Time challenge	++	++	++	?	?	?	-	-	?
Potency	+++	++	++	++	+	++	++	+	+

(+/-)=equivocal results, (?)=few data available, (-)=no or decreased effect, (+)=increased effect, NA=not applicable

As Insulin is a lifesaving drug, it should be on the top of list. Biguanides have stood the challenge of time, proved safe, effective and protective against cancer, microvascular and macrovascular complications. The rare serious side effect of lactic acidosis is negated in many trials.

Although Gliptins and GLP-1 analogues represent a different hypoglycemic action and preserve the β-cells, the use of GLP-1 is less plausible because it is parenterally administered.

TZDs have encountered major drawback in its clinical trial; therefore, it was excluded. Neglitides and Acarbose were not desirable by patients for documented side effects and long-term studies are awaited to prove their protective effect. Amylin analogues are new medications and long term studies of tolerance and effectiveness are awaited.

Even though, some Sulfonylureas are experiencing drawbacks in relation to microvascular complications, the class had stood the challenge of time and some of its members are actually showing improved structure and function.

## CONCLUSION

**The goals of diabetes treatment are to maintain patient's quality of life close to the healthy people. Antidiabetic drugs are expected to correct abnormalities primarily in glucose metabolism<sup>20</sup>.**

**The ideal drug should reduce hyperglycemia without inducing hypoglycemia, increase β-cell mass, increase insulin sensitivity, maintain or even decrease weight, decrease**

**microvascular and macrovascular complications, is not carcinogenic, plausible to users (adherence to therapy) and stands the challenge of time.**

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