

# Diabetes Beyond Insulin: Review of New Drugs for Treatment of Diabetes Mellitus

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**Abstract:** Diabetes mellitus (DM) is a progressive disease characterized by insulin deficiency and insulin resistance or both. The fasting and post-prandial blood glucose is elevated, exposing the patient to acute and chronic complications (micro- and macro-vascular) leading to blindness, kidney failure, heart disease, stroke and amputations. Improving glycemic control has been demonstrated to lower the risk of these complications. Owing to the progressive nature of the disease, an evolving treatment strategy is necessary to maintain glycemic control.

Varieties of new pharmacologic interventions are developed in past 5 years to treat people with diabetes. Several studies have been carried out covering different aspects of pharmacological interventions (newer and old drugs) along with the effects of weight loss, diet and exercise. Two categories of drugs have been used for the treatment of Diabetes Mellitus: the insulin and oral agents. Insulin analogues are molecules that differ from human insulin in amino acid sequence but bind to the insulin receptors and act similarly in function.

This article provides an update of pharmacologic interventions for diabetes with practical overview of the new drug options, new insulin analogues, pharmacology, clinical efficacy, safety, dosing, cost, with specific examples of each and their background and side effects used to achieve tight glucose control. These agents have distinct characteristics that help in their selection for the treatment of type 1 and type 2 diabetes.

**Key Words:** Diabetes Mellitus (DM), type-1 diabetes, type-2 diabetes, thiazolidinediones, insulin secretagogues, biguanides, glucosidase inhibitors, meglitinide analogues, HbA1c, incretin.

## INTRODUCTION

Diabetes mellitus is one of the most prevalent and serious diseases in the United States. Diabetes mellitus affects approximately 19 million people in the United States and approximately 135 million people world wide and accounts for about one fifth of all expenditures for health care. A chronic ailment that impairs the production of or response to insulin, a hormone that helps converts food into energy. It is estimated that the number of people with this disorder will double worldwide by the year 2010. The prevalence of diabetes continues to increase steadily as more people live longer and grow heavier. Type-1 diabetes comprises those forms of diabetes that are primarily due to insulin deficiency. Type-2 diabetes comprises those forms that result from a primary defect in insulin resistance (often associated with obesity), coupled with a relative insulin deficiency. Eventually, progressive loss of  $\beta$ -cell function in type-2 diabetes creates an absolute insulin deficiency becomes complicated by glucose (glucosamine) and lipid mediated toxicities. These complications decrease the patients' abilities to secrete insulin to the point where it becomes a diagnostic confusion with type-1 diabetes.

The overall prevalence of diagnosed cases of type 2 diabetes is approximately 2.4 percent between the ages 25 of 44

years, 5.6 percent between the ages of 45 and 54 years and 8.8 percent between the ages of 55 and 64 years and over 10 percent over the age of 65 years. The prevalence may be well over 20 percent among frail elderly people living in nursing homes. There are probably similar numbers of undiagnosed patients at all ages. Together they contribute to about 200,000 deaths a year. Diabetes is also the leading cause of end-stage renal disease, blindness in adults, and lower-limb amputations. [1-4]. Diabetes is defined by the glycemic threshold as documented in population-based studies. Population studies have defined cut-off levels of glycemia that are eventually associated with increased micro-vascular disease, such as retinopathy. Two replicate fasting levels that exceed 126 mg/dl ( $>7$  mmol/L) are diagnostic in the absence of symptoms. The new 2003 ADA's definition of the cut point for normal fasting blood glucose levels was dropped from 110 mg/dl to 100 mg/dl, meaning that a value of 100 mg/dl or above would lead to a diagnosis of impaired fasting glucose (IFG), which is included in the term pre-diabetes. Persons with impaired fasting plasma glucose (FPG) levels (FPG= 100-125 mg/dl (5.66-6.9 mmol/L) and/or with impaired glucose tolerance test (IGT) (2 hour post-load glucose 140-199 mg/dl (7.8-11.1 mmol/L) are at risk of diabetes and should be observed periodically to detect progression to overt diabetes. Replicate, two-hour glycemic responses  $>200$  mg/dl ( $>11.1$  mmol/L) after a standard oral glucose tolerance test also indicates diabetes. However, this stage is often reached before the fasting glucose levels rise. Indeed post-prandial hyperglycemia may precede fasting hypergly-

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**Table 1. The American Diabetes Association (ADA) Guidelines for the Evaluation of Glucose Level to Diagnose or Predict Diabetes**

Glucose Level	ADA Evaluation
Normal	Fasting plasma glucose (FPG) <100 mg/dL (5.6 mmol/L), HbA <sub>1c</sub> <6
Impaired Glucose Tolerance (IGT)	Fasting plasma glucose (FPG) <sup>3</sup> 100 (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L) or two-hour plasma glucose level of <sup>3</sup> 140 mg/dl (7.8 mmol/L) but <200 mg/dl (11.1 mmol/L), HbA <sub>1c</sub> <7
Diabetes mellitus	Fasting plasma glucose FPG =126 mg/dL (7.0 mmol/L) or randomly (or 2 hr OGTT value) = 200 mg/dL (11.1 mmol), HbA <sub>1c</sub> >8

chemia by months to years. The American Diabetes Association (ADA) glycemic criteria for type 2 diabetes mellitus prediction and diagnosis to initiate the treatment are shown in Table 1.

Ninety percent of patients with diabetes have type-2 diabetes (formerly known as non-insulin-dependent diabetes) and often require oral agents or insulin for glucose control. The mortality rate in patients with diabetes may be up to 11 times higher than in persons without the disease.

Current treatments, however, do not satisfactorily control a glucose level, which is the primary purpose, nor do they prevent complications.

There are currently several classes of drugs on the market, including insulin, for treatment of diabetes with total worldwide revenues in the \$20B range. Within the past three years, the introduction of many new oral agents has prompted questions regarding the most effective approach for management of type 2 diabetes [5-7].

Not everybody optimally responds to each medication and not everybody can tolerate each medication. So having new treatment options and combination of multiple new drugs in a new class for such a widely prevalent disease are important. Since pharmaco-economic data concerning anti-diabetic regimens are limited, clinicians must select the most appropriate agent(s) based on patient characteristics, level of glucose control and cost. A rational approach for managing patients with varying stages of disease requires an understanding of features that lead to disease progression, and a thorough review of the new oral agents for the treatment of type-2 diabetes and the clinical and economic basis for appropriate drug selection. Today, better understanding of the pathophysiology of the disease leads to the development of more effective treatment options. At present, at least six different major forms of therapy are available for T2DM: lifestyle modifications of diet and exercise, insulin replacement therapy, insulin secretagogues, biguanides, meglitinides,  $\alpha$ -glucosidase inhibitors, and PPAR- $\gamma$  agonists. These options provide a huge number of possible combinations. To achieve good glucose control and prevent complications of diabetes, patients usually are on multiple drug combinations.

The primary goal of this review is to describe various new developments in treatment of diabetes. This article outlines in detail the description of the treatment options including relieving symptoms, optimizing glycemic control to pre-

vent complications, thereby maintaining and/or enhancing the quality of life, while at the same time avoiding debilitating side effects of treatment.

### **NEW DRUGS FOR TYPE 2 DIABETES; DRUGS THAT PROMOTE THE BODY'S PRODUCTION OF INSULIN (INSULIN SECRETAGOGUES): SULFONYLUREAS**

Sulfonylureas have been available since many years and are classified as either first- or second-generation agents. The second generations differ in potency, safety, and pharmacokinetics. The second-generation agents are more potent and have better pharmacokinetic and safety profiles.

The first-generation agents include acetohexamide (Dymelor®), chlorpropamide (Diabinese®), tolazamide (Tolinase®), and tolbutamide (Orinase®). The second-generation agents include glimepiride (Amaryl®), glipizide (Glucotrol®), and glyburide (Diabeta®, Micronase®, Glynase®).

Sulfonylureas lower FPG primarily by increasing the release of insulin from functioning pancreatic  $\beta$  cells. They display a glucose-dependent effect. Loss of efficacy over time is a major concern with the use of sulfonylureas. This appears to be related to exhaustion of  $\beta$ -cell function. Sulfonylureas increase plasma levels of insulin and cause hypoglycemia. They reduce FPG by about 60 to 70 mg/dL (3.4-3.9 mmol/L) and A1C by 1.5% to 2.0% at maximally effective doses. Sulfonylureas do not have a significant effect on lipids. Hypoglycemia and weight gain are the two most frequent side effects of these drugs. Hypoglycemia is especially a problem with the first-generation agents because of their long half-lives. Elderly individuals, people who frequently skip meals, and people who perform frequent intense exercise are most susceptible. In the United Kingdom Prospective Diabetes Study (UKPDS), sulfonylureas were associated with a decrease in microvascular events compared to diet treatment, but there was no significant difference in mortality or macrovascular events [8-14]. The lack of benefit on cardiovascular complications may be related to the fact that they cause hyperinsulinemia, which is associated with the metabolic syndrome.

Doses; Glimepiride (Amaryl®), 1-8 mg; (Glucotrol®), 2.5-40 mg ; (Glucotrol XL®), 5-20 mg; Diabeta®, Micronase®, 2.5-20 mg; Micronized glyburide (Glynase®), 0.75-12 mg.

## NON-SULFONYLUREA SECRETAGOGUES (MEGLITINIDE ANALOGUES; BENZOIC ACID DERIVATIVES)

The meglitinide analogs, including nateglinide (Starlix) and repaglinide (Prandin), are nonsulfonylurea secretagogues (available since 2000) that also bind to  $K_{ATP}$  channels, albeit at a different site than traditional sulfonylureas. These agents stimulate the release of insulin from pancreatic  $\beta$  cells if glucose is present. In general, meglitinide analogs have much shorter half-lives than do sulfonylureas. Nateglinide (Starlix) is a new meglitinide analogue and a derivative of *D*-phenylalanine. Nateglinide mimics physiologic insulin secretion dynamics seen in healthy individuals by increasing early phase insulin secretion into the portal vein and in that way increases hepatic glucose uptake as well as hepatic glucose suppression. In contrast to sulfonylureas and repaglinide, nateglinide is a more potent agent to restore early phase insulin release with less hypoglycemia episodes. When administered before meals, nateglinide rapidly acts at the same pancreatic  $\beta$ -cell  $K_{ATP}$  channel as sulfonylureas and repaglinide but dissociates from the receptor within seconds. Therefore, delayed hyperinsulinemia and an increased risk of hypoglycemia are unlikely with nateglinide. Clinical trials have demonstrated that nateglinide can reduce postprandial hyperglycemia and thereby improve glycemic control.

Whether the meglitinide analogs have adverse effects on ischemic preconditioning is not known. However, both nateglinide and repaglinide have plasma half-lives of <2 h, and plasma insulin decreases to basal levels within 2 h after an oral dose. Thus, even if one or both of these agents was found to have an adverse effect on ischemic preconditioning, their short half-lives would tend to minimize this effect [15-20]. In addition, studies are on-going to determine the net effect (i.e., positive, negative, or neutral) of these agents on cardiovascular outcomes in patients with Type 2 diabetes.

Repaglinide and nateglinide reduce FPG by about 65 to 75 mg/dL (3.6-4.2 mmol/L) and A1C by about 1.5% to 2.0% and 0.5% to 1.5%, respectively. They have a short half-life, so they stimulate insulin release for brief episodes. The quick on and off helps decrease hypoglycemia, hyperinsulinemia, weight gain, and possible  $\beta$ -cell exhaustion compared to sulfonylureas [15-19]. Dosed prior to meals, the maximal effect on glucose occurs postprandially. Meglitinides have no effect on lipids. Repaglinide should be initiated at 0.5 mg 3 times daily orally and titrated up to a maximum daily dose of 16 mg. Most of the benefit is achieved with 1 mg 3 times daily. Nateglinide should be initiated at 60 mg 3 times daily orally and titrated up to a maximum daily dose of 360 mg. Doses should be taken 15 to 30 minutes prior to meals. These agents are useful for people with high postprandial glucose levels and/or irregular meal schedules.

## BIGUANIDES; DRUGS THAT REDUCE GLUCOSE PRODUCTION BY THE LIVER

### Metformin

Metformin is not a new medication, although it was only approved by the FDA for use in the United States in 1995. Its primary effect is to inhibit the liver's production of glu-

cose and, possibly, to stimulate the process of transporting glucose into muscle, a process which requires insulin. Thus it only works when there is insulin around, for example in type 2 diabetes, but not in type-1 diabetes, which is characterized by total insulin dependency. However, many studies indicated that Metformin is helpful in increasing the insulin sensitivity even in Type-1 diabetes and may assist in insulin dose reduction. Exactly how Metformin works is not well understood. Metformin can be used as a first line of therapy. The large study United Kingdom Prospective Diabetes Study (UKPDS) revealed that diabetes is a progressive disease with complications that are directly proportional to the level of glycemic control. Concomitant with the inexorable decline in endogenous insulin secretion in the UKPDS was a progressive increase in hyperglycemia, and HbA<sub>1C</sub> levels regardless of the mode of treatment given. The study results reported that the patients who were treated rigorously with sulfonylurea and Metformin showed significant improvements in the glycemic control and hyperlipidemia and had delayed diabetes related complications. With over 10 years of follow-up, intensive therapy resulted in an absolute 1% reduction in HbA<sub>1C</sub> value over conventional therapy. The 11% difference in HbA<sub>1C</sub> was associated with a 12% lower risk in aggregate diabetes outcomes, with most of the reduction based on a 25% reduction in micro-vascular disease such as in retinopathy and nephropathy [3]. Furthermore, obese patients in the UKPDS who were assigned initially to receive metformin rather than sulfonylurea or insulin therapy had a decreased risk of any diabetes-related endpoint and mortalities from all causes. Thus Metformin is useful for patients who are obese as it does not promote the weight gain as seen with sulfonylureas, it may even bring about some degree of weight loss [21-28]. Metformin is also as capable as the sulfonylureas in reducing HbA<sub>1c</sub>. An additional benefit of metformin is its positive effect upon lipid metabolism and it reduces blood triglyceride and LDL (the "bad") cholesterol levels by about 10% and also lowers fatty acids.

Side effects can be a problem with metformin. Up to 30% of patients develop gastrointestinal complaints, though these may be mild and temporary, especially if dosages are brought up slowly. Bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints. The largest concern with metformin is the potential to produce a build up of lactic acid. However, this is a very rare side effect of the drug, particularly if care is taken not to prescribe metformin when it is contraindicated. Contraindications for this drug include evidence of kidney disease, significant liver disease, chronic alcoholism or congestive heart failure. Hypoglycemia and, as mentioned above, weight gain, are not on the list of metformin's side effects. Metformin should be initiated at 500 mg orally twice daily, with the 2 largest meals of the day to minimize GI effects and beneficial effects can be seen within 1 week. The dose can be titrated every 2 weeks up to 2000 mg daily. Extended-release metformin is an important addition to the formulary which reduces side effects and improves compliance with once a day dosing, as well as because of the reduction in G.I. side effects as less frequent dosing schedules and probably in many cases less medication is required as the drug is released slowly over the longer time duration opposed to quick released form.

## DRUGS THAT HELP THE BODY RESPOND TO INSULIN (INSULIN SENSITIZERS)

### Thiazolidinediones

The thiazolidinediones (TZDs) enhance insulin action in muscle, fat and other tissues and are known as insulin sensitizers. They require the presence of insulin in order to work. To a lesser extent, they decrease hepatic glucose production. TZDs are selective and potent agonists for the peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ) nuclear receptors. Activation of these receptors regulates the transcription of insulin-responsive genes involved in the control of production, transport, and use of glucose. The action of these agents requires the presence of insulin. TZDs may also improve  $\beta$ -cell function by reducing free fatty acids. They do not directly affect insulin secretion, so they are not associated with hypoglycemia. TZDs are effective in reducing HbA1c. They are also effective in combination with either sulfonylureas or metformin. Compared to other drugs, it takes a patient a long time to see the benefits of the TZDs. For this reason, doses should not be increased until after 4-6 weeks, the time it normally takes for maximal biological effect to occur. About 25% of patients do not respond to TZDs. Some TZDs also have beneficial effects on blood lipids. Troglitazone has a lipid lowering effect and increases HDL, or high-density lipoprotein (the good cholesterol). Pioglitazone also decreases triglycerides [29-38].

The major side effect, TZDs are associated with edema and weight gain. The weight gain may be due to a change in fat distribution with an increase in subcutaneous adipose fat and a decrease in visceral fat. It could also be due to an increase in plasma volume (i.e., edema). The edema is thought to be due to a decrease in renal excretion of sodium and an increase in sodium and free water retention. Pedal edema occurs in 3% to 5% of people taking TZDs. The incidence is greater when they are used with other glucose-lowering agents. Pioglitazone is initiated at 15 mg orally daily and titrated up every 3 to 4 weeks to a maximum dose of 45 mg. Rosiglitazone's starting dose is 4 mg once daily or 2 mg twice daily and is titrated up at the same interval as pioglitazone to a maximum of 8 mg/d. TZDs have a slow onset of action, so the full effect may not be seen for up to 4 months. People with known insulin resistance and/or a contraindication to metformin may find TZDs of benefit. Because of the associated risk of heart failure, the American Heart Association and the ADA recommend assessing for risk factors for heart failure before starting diabetic patients on a TZD; using these agents cautiously (i.e., starting at low doses and titrating upward slowly and carefully while monitoring for symptoms) in patients who have such risk factors or who have asymptomatic or mildly symptomatic heart failure; and avoiding TZDs in patients with New York Heart Association class III or IV heart failure. Recently, there are many reports of adverse events of Rosiglitazone use and the therapy is now questionable. More studies are in progress to confirm this fact.

## DRUGS THAT REDUCE POSTPRANDIAL GLUCOSE CONCENTRATIONS

### $\alpha$ -Glucosidase Inhibitors

The  $\alpha$ -glucosidase inhibitors have been available since 1996 and include acarbose (Precose®) and miglitol (Glyset®). These drugs slow down the rate of carbohydrate absorption in the small intestine, which results primarily in a reduction in postprandial plasma glucose levels. They act as competitive, reversible inhibitors of  $\alpha$ -glucosidase (found in the small intestine) and  $\alpha$ -amylase (found in the pancreas), which convert non absorbable dietary starch and sucrose into absorbable glucose and hydrolyze complex starches, respectively. These agents do not affect insulin levels, so they do not cause hypoglycemia when used alone. When  $\alpha$ -glucosidase inhibitors are used with another antihyperglycemic agent (i.e., sulfonylureas) and hypoglycemia occurs, the hypoglycemia needs to be reversed by ingesting glucose (tablets or gels), not complex carbohydrates. Complex carbohydrates would be slowly broken down by the  $\alpha$ -glucosidase inhibitor and thus would not be effective in quickly relieving hypoglycemia.

These medicines are not usually used for primary therapy unless a patient appears to have large increases in blood glucose after meals ("postprandial").  $\alpha$ -Glucosidase inhibitors are most useful in combination with other drugs [39-42]. Gastrointestinal side effects are common, affecting up to 30% of patients. Bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints. However, these side effects can be reduced by eating less carbohydrate in the diet. Hypoglycemia is not often seen but, if the patient develops low blood glucose levels, he/she must be treated with glucose, not complex carbohydrates. This is because the action of these drugs, which prevent breakdown of complex carbohydrates in the intestine, will be unable to rapidly correct blood glucose concentrations. Weight gain does not occur with these drugs.

Doses; Acarbose (Precose®), 25-100 mg with meals; Miglitol (Glyset®), 25-100 mg with meals.

## MULTI DRUGS THERAPY OR COMBINATION THERAPY

As mentioned above, primary therapy can begin with a sulfonylurea or metformin and the goal of therapy is to achieve ADA guidelines for glucose control. If treatment with one drug fails to achieve this goal, i.e., monotherapy does not achieve glycemic levels goal because of noncompliance, combination therapy is used because diabetes is a progressive disease. Most of the drug classes can be combined, except sulfonylureas and non-sulfonylurea insulin secretagogues since they have the same mechanism of action. There are combination tablets that have been formulated to allow for a decreased pill burden. If combination oral therapy does not achieve glycemic goals, insulin should be initiated [43-44]. The Table 2 summarizes the actions of each agent with the site of their actions and possible side effects.

Table 2. Oral Agents with Mechanism of Action and Side Effects

Oral Antidiabetics	Mechanism of Action	Side Effects
<b>Sulfonylureas</b> Glimiperide (Amaryl) Glipizide (Glucotrol) Glipizide-gits (Glucotrol-XL) Glyburide (Diabeta, Micronase) Glyburide micronized (Glynase) Tolbutamide (Orinase) Chlorpropamide (Diabinese) Tolazamide (Tolinase) Acetohexamide (Dymelor)	Stimulate first-phase insulin secretion by blocking K <sup>+</sup> channel in $\beta$ -cells.	Late hyperinsulinemia and hypoglycemia Weight gain
<b>Meglitinides</b> Repaglinide (Prandin) Nateglinide (Starlix)	Stimulate first-phase insulin secretion by blocking K <sup>+</sup> channel in $\beta$ -cells.	Hypoglycemia Weight gain
<b>Biguanides</b> Metformin (Glucophage, Riomet) Metformin-XR (Glucophage-XR)	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea, Diarrhea Anorexia, Lactic acidosis
<b>Thiazolidinediones</b> Rosiglitazone (Avandia) Pioglitazone (Actos)	Increase insulin sensitivity via activation of PPAR-g receptors	Fluid retention and weight gain
<b><math>\alpha</math>-Glucoside Inhibitors</b> Acarbose (Precose) Miglitol (Glyset)	Decrease hepatic glucose production Delays glucose absorption	Flatulence Abdominal bloating

## NEW PRODUCTS

### Inhaled Insulin

Exubera® was approved for use by the FDA in January 2006. It is short acting insulin used immediately before meals to lower blood sugar. There are three other insulin products in development as well. Inhaled insulin could replace insulin injections. Moreover, in Type 2 diabetes it could reduce the number of oral antidiabetic drugs required, since patients would be more likely to accept insulin at an earlier stage in their treatment regimen and improve their adherence to therapy [45]. The long-term effects of this therapy under investigation for possible lungs damage and side effects like pulmonary fibrosis etc.

Several methods of insulin delivery have been researched with varying results. A transdermal delivery of insulin produces insufficient transfer of insulin across the skin. Oral insulin is not bioavailable and is broken down in the gut. New Oral Insulin Spray (buccal spray) form is still under the clinical investigation. Intranasal insulin also produces poor bioavailability and unpredictable variability in dosing with a short metabolic effect.

### Byetta

Byetta (Exenatide) was developed to improve glucose control in patients with type 2 diabetes who are not achieving target goals with current treatment regimens. It is admin-

istered by twice-daily subcutaneous injections. The US FDA approved Byetta in April 2005 for use in conjunction with other diabetes medications, but not as a stand-alone medicine.

Byetta's active ingredient mimics a hormone found in the saliva of the poisonous Gila monster, the largest lizard native to North America, and the human gut polypeptide called glucagon-like peptide 1 (GLP-1). This substance decreases a person's appetite and slows down gastric emptying leading to weight loss. Moreover, it enhances the ability of the body to dispose of extra glucose in the blood stream after meals. Long-term, it may even promote new production of beta cells in the pancreas [46-49].

### Symlin®

Symlin® (Pramlintide Acetate) is a synthetic version of human amylin, a hormone produced along with insulin by the beta cells in the pancreas. Symlin® has been studied for treatment in patients with type 1 diabetes or insulin requiring type 2 diabetes. Patients inject it subcutaneously before meals. In March 2005, the US FDA approved its use only in conjunction with insulin injections. The action this drug depends on the presence of insulin in the body [50-51].

### New Indications

The US FDA has approved Bristol-Myers Squibb's Glucophage® (metformin) for use in children. This is of particu-

lar importance with the increasing prevalence of Type 2 diabetes in children.

#### **New Drug Class: Dipeptidyl Peptidase-4 (DPP-4)**

Januvia® (Sitagliptin) was approved by the FDA in October 2006 for use in people with Type 2 diabetes. It can be used alone, with metformin or a thiazolidinediones, and is well tolerated. It is the first of a new type of drug to treat Type 2 diabetes. It helps the body respond to glucose from a meal by increasing insulin levels and adjusting other hormones. [52-56].

#### **Insulins**

Several "designer" insulins are either fast acting or very slow acting, which makes it easier for those who need insulin to control their sugars at rest or at mealtimes. These include the rapid-acting insulin products Humalog®, Novolog®, and Apidra®; and the long-acting products Lantus® and Levemir®.

#### **Insulin Lispro**

Introduced in 1996, lispro differs from human insulin by a switch at lysine B28 and proline B29. In the vial, the lispro exists as a hexameric formulation, but when it is injected, it dissociates into a monomeric formulation, leading to a more rapid absorption and shorter duration of action. Patients using lispro are able to use less insulin and experience fewer hypoglycemic events. Lispro has been beneficial in patients with end-stage renal disease patients and in pregnant patients [57-61].

#### **Insulin Aspart**

Aspart is the newest rapid-acting insulin analog; it differs from human insulin through substitution of aspartic acid at B28. The time to maximum concentration is 52 minutes vs 145 minutes with regular insulin. Aspart has shown better PPG control and less nocturnal hypoglycemia compared with regular insulin. A small study comparing aspart and lispro demonstrated them to be very similar; however, lispro peaked approximately 10 minutes earlier.

#### **Insulin Glargine**

Glargine differs from human insulin by replacing asparagine at A21 with glycine and adding 2 arginines to the C-terminus of the B-chain. Glargine was designed to mimic normal basal insulin, with a slow absorption and long half-life. Glargine is stable at a pH of 4 and will precipitate at physiologic pH, thereby causing the slow absorption. Glargine was shown to cause less nocturnal hypoglycemia in patients with type 1 diabetes. Also, the pre- and postprandial blood glucose levels were lower in the glargine group vs NPH [62-63].

When converting once-daily NPH dosing, the glargine dose would be the same. When converting from a twice-daily NPH dose to glargine, the dose should be decreased by 20%. If converting from ultralente insulin to insulin glargine, the dose should be reduced to one third or one half on day 1 and then titrated to the full dose on day 2. Most experts start a new patient on 10 units of glargine at bedtime. Patients

may need fewer snacks when using glargine because there is a lower incidence of hypoglycemia with this analog. Due to the acidic pH, patients may experience a slight sting upon injection. A number of pen-type devices have also been designed to make it easier for someone to take their insulin more accurately and conveniently.

#### **Incretins**

Researchers have now identified other products manufactured by our bodies that stimulate the beta cells to release insulin. The term "incretins" refers to secretory products of the intestine that influence beta cell function. These proteins, GIP and GLP-1, enhance insulin secretion [64].

#### **GIP**

GIP is a 42-amino acid peptide that is secreted by the K-cells of the intestine located primarily in the small intestine. After a meal, scientists found that blood levels of GIP rise within minutes. GIP was also found to have a variety of effects on fat metabolism. Though GIP seems to operate in healthy individuals, it has limited usefulness for diabetic individuals with higher than normal blood sugar levels.

#### **GLP-1**

(Glucagons like peptide), in contrast, works in everyone. GLP-1 exists in two forms, a 30- and a 31-amino acid peptide, and is secreted by the L-cells of the large bowel and the last section of the small bowel. Most amazingly, GLP-1 is secreted within minutes of eating food even though these distant L-cells have not been in contact with food. This rapid response to food ingestion implies that some kind of nerve pathway is involved. As with GIP, GLP-1 levels are low in the fasting state, rises after eating but, unlike GIP, GLP-1 can affect insulin secretion even in patients with Type 2 diabetes. What this means is that GLP-1 may help diabetics individuals better regulate their blood sugar through more effective insulin release. The recognition of the key role played by GLP-1 in glucose regulation has led to attempts to develop drug therapies that mimic or enhance GLP-1 activity [66]. Exenatide, a naturally occurring product, originally isolated from the saliva of the Gila monster, is very similar to human GLP-1. It is administered by subcutaneous injection, typically at a dose of 10 mcg twice a day. By itself or in combination with sulfonylureas, metformin or combination sulfonylurea/metformin, exenatide can lower blood glucose levels. Remarkably, exenatide also causes weight loss in contrast to the weight gain typically seen with insulin, as well as with most oral antidiabetic medications.

#### **CONCLUSIONS: THE FUTURE**

The prognosis of type-1 diabetes continues to improve with advances in home blood monitoring, basal insulins with modest peaks of action and insulin delivery systems exemplified by insulin pumps. Type-2 diabetes has emerged as the more serious form of diabetes, while prevention of it through attention to the predisposing factors is looming increasingly important to our public health. There will be an increase in the proportion of the population diagnosed with Type 2 dia-

betes and also a greater awareness of impaired glucose tolerance and dysmetabolic syndrome. Dysmetabolic syndrome is perhaps the single biggest health care issue in North America and individuals with this syndrome are at high risk of diabetes and heart disease. The US obesity epidemic continues unabated, with ever increasing numbers of the nation's obese children becoming irreversibly obese adults, replete with the insulin resistance in all of its' burgeoning complications, notably of progressive atherosclerotic disease, hypertension and type-2 diabetes. Patients will be diagnosed much earlier and treated more aggressively to stop these conditions from developing. The only rational long term solution must lie in the realization that the epidemic interventional focus should be placed in early life.

## REFERENCES

- [1] American Diabetes Association, Standard of medical care in diabetes. *Diabetes Care* 29: S4–S42 (2006).
- [2] Institute for Clinical Systems Improvement (ICSI) Management of type 2 diabetes mellitus, Bloomington, Minnesota Institute for Clinical Systems Improvement (ICSI) pp. 79 (2005).
- [3] Davies M.J., Tringham J.R., Troughton J., Khunti K.K.: *Prevention of type 2 diabetes mellitus, A review of the evidence and its application in a UK setting.* *Diabet. Med.* 21: 403-14 (2004).
- [4] American Diabetes Association, Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care* 26 (suppl 1), S28 -S32, (2003).
- [5] IDF Clinical Guidelines Task Force, Global guideline for Type 2 diabetes. International Diabetes Federation Conference, Brussels, (2005).
- [6] Wickersham R.M., Novak K.K., Eds.; *Drug Facts and Comparisons*; Wolter Kluwer: St. Louis, Montana, (2006).
- [7] Average wholesale prices. [www.drugstore.com/pharmacy/drugindex](http://www.drugstore.com/pharmacy/drugindex): Accessed June 4, (2007).
- [8] Epocrates Drug Database. [www2.epocrates.com/index.html](http://www2.epocrates.com/index.html): (2007).
- [9] Turner R.C., Cull C.A., Frighi V., Avery L.: *Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus, progressive requirement for multiple therapies (UKPDS 40).* *JAMA* 281, 2005-2012, (1999).
- [10] Inzucchi S.E.: *Oral antihyperglycemic therapy for type 2 diabetes.* *JAMA* 287, 360–372, (2002).
- [11] Klam Cheri, Neher Jon, Mayo Helen.: *What is the best medical therapy for new-onset Type-2 diabetes?* *J. Fam. Pract.* 55(11), 998-1000, (2006).
- [12] Renee R.K.: *Practical Review of Oral Antihyperglycemic Agents for Type 2 Diabetes Mellitus.* *Diabetes Educ.* 32(6) 869-876, (2006).
- [13] DeFronzo R.A.: *Pharmacologic therapy for type 2 diabetes mellitus,* *Ann. Intern. Med.* 131(4), 281-303, (1999).
- [14] Bryan J., Crane A., Vila-Carriles W.H., Babenko A.P., Aguilar-Bryan L.: *Insulin Secretagogues, Sulfonylurea Receptors and KATP Channels.* *Curr. Pharma. Design* 21 (11), 2699-2716, (2005).
- [15] Bloomgarden Z.T.: *New Therapeutic Approaches To Non-Insulin-Dependent Diabetes Mellitus.* *Endocrine Practice* 5(3), 307-312, (1997).
- [16] KAD R.D.: *Mitiglinide.* *Drugs* (5)98-101, (2004).
- [17] Phillips L.S., Dunning B.E.: *Nateglinide (Starlix™), Update on a new antihyperglycemic agent.* *Int. J. Clin. Pract.* 57, 535 -541, (2003).
- [18] Dornhorst A.: *Insulinotropic meglitinide analogue.* *Lancet* 358, 1709-1716, (2001).
- [19] Prandin.: *Physicians' Desk Reference [electronic version],* Thomson Micromedex: Colorado, (2006).
- [20] Starlix.: *Physicians' Desk Reference [electronic version].* Thomson Micromedex: Colorado, (2006).
- [21] Caulfield M., O'Brien K.: *Cardiovascular Safety of Oral Antidiabetic Agents, The Insulin Secretagogues.* *Clinical Diabetes* 20, 81-84, (2002).
- [22] Saenz A., Fernandez-Esteban I., Mataix A., Ausejo M., Roque M., Moher D.: *Metformin monotherapy for type 2 diabetes mellitus.* *Cochrane Database Syst. Rev.* (3) (2005).
- [23] UK Prospective Diabetes Study (UKPDS) Group, *Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS34).* *Lancet* 352, 854–865, (1998).
- [24] Saenz A., Fernandez-Esteban I., Mataix A.: *Metformin monotherapy for type 2 diabetes mellitus,* *Cochrane Metabolic and Endocrine Disorders Group.* *Cochrane Database Syst. Rev.* (3) (2005).
- [25] Wulffele M.G., Kooy A., De Zeeuw D.: *The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus; a systematic review.* *J. Intern. Med.* (256)1 (2004).
- [26] Johnson J.A., Simpson S.H., Toth E.L.: *Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes.* *Diabet. Med.* (22)497-502, (2005).
- [27] Kirpichnikov D., McFarlane S.I., Sowers J.R.: *Metformin, an update.* *Ann. Intern. Med.* 137, 25-33, (2002).
- [28] Salpeter S.R., Greyber E., Pasternak G.A.: *Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus.* *Arch. Intern. Med.* 163, 2594-2602, (2003).
- [29] Glucophage. *Physicians' Desk Reference [electronic version].* Thomson Micromedex: Colorado, (2006).
- [30] Shimabukuro M., Zhou Y-T., Lee Y.: *Troglitazone lowers islet fat and restores beta cell function of Zucker diabetic fatty rats.* *J. Biol. Chem.* (273)3547-3550, (1998).

- [31] Chiquette E., Ramirez G., DeFronzo R.: *A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors*. Arch. Intern. Med. 164, 2097-2104, (2004).
- [32] Ahmann A.J., Riddle M.C.: *Current oral agents for type 2 diabetes; many options, but which one to choose when?* Postgrad. Med. 111, 32-46, (2002).
- [33] Dormandy J.A., Charbonnel B., Eckland D.J.: *Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomized controlled trial*. Lancet 366, 1279-1289, (2005).
- [34] Choi D., Kim S.K., Choi S.H.: *Preventative effects of Rosiglitazone on restenosis after coronary stent implantation in patients with type 2 diabetes*. Diabetes Care 27, 2654-2660, (2004).
- [35] Nesto R.W., Bell D., Bonow R.O.: *Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association*. Diabetes Care 27, 256-263, (2004).
- [36] Glitazone-associated macular edema. *Pharmacist's Letter/Prescriber's Letter* 22, 220-205, (2006).
- [37] Effect of Rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Lancet 368, 666, (2006).
- [38] Scheen A.J.: Hepatotoxicity with thiazolidinediones: is it a class effect? *Drug Saf.* 24, 873-888, (2001).
- [39] Avandia.: *Physicians' Desk Reference* [electronic version], Thomson Micromedex, (2006).
- [40] Actos.: *Physicians' Desk Reference* [electronic version], Thomson Micromedex; (2006).
- [41] Van de Laar F.A., Lucassen P.L.B.J., Akkermans R.P., Van de Lisdonk E.H., Rutten G.E.H.M., Can W.C.: *Alpha-glucosidase inhibitors for type 2 diabetes mellitus*. Cochrane. Database Syst. Rev. 2, (2005).
- [42] Van der Laar F.A., Lucassen P.L.B.J., Akkermans R.P.: *Alpha-glucosidase inhibitors for type 2 diabetes mellitus*. *Cochrane Metabolic and Endocrine Disorders Group*, Cochrane Database Syst. Rev. 2, (2005).
- [43] Precose.: *Physicians' Desk Reference* [electronic version]. Thomson Micromedex, (2006).
- [44] Glyset.: *Physicians' Desk Reference* [electronic version]. Thomson Micromedex, (2006).
- [45] Yamanouchi T., Sakai T., Igarashi K., Ichianagi K., Watanabe H., Kawasaki T.: *Comparison of metabolic effects of pioglitazone, metformin, and glimepiride over 1 year in Japanese patients with newly diagnosed Type 2 diabetes*. Diabet. Med. 22, 980-985, (2005)
- [46] Browne D.L., Avery L., Turner B.C.: *What do patients with diabetes know about their tablets?* Diabet. Med. 17, 528-531, (2000).
- [47] DeFronzo R.A., Bergenstal R.M., Cefalu W.T.: *Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise*. Diabetes Care 28, 1922-1928, (2005).
- [48] DeFronzo R.A., Ratner R.E., Han J., Kim D.D., Fine-man M.S., Baron A.D.: *Effects of exenatide(exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes*. Diabetes Care 28(5), 1092-100, (2005).
- [49] Calara F., Taylor K., Han J., Zabala E., Carr E.M., Wintle M., Fineman M.: *A randomized, open-label, crossover study examining the effect of injection site on bioavailability of exenatide (synthetic exendin-4)*. Clin. Ther. 27(2), 210-215, (2005).
- [50] Nauck M.A., Meier J.J.: *Glucagon-like peptide 1 and its derivatives in the treatment of diabetes*. Regul. Pept. 128(2), 135-48, (2005).
- [51] Gedulin B.R., Nikoulina S.E., Smith P.A., Gedulin G., Nielsen L.L., Baron A.D., Parkes D.G., Young A.A.: *Exenatide (exendin-4) improves insulin sensitivity and  $\beta$ -cell mass in insulin-resistant obese fa/fa Zucker rats independent of glycemia and body weight*. Endocrinology 146(4), 2069-76, (2005).
- [52] Young A.: *Selected Studies About Symli*. Adv. Pharmacol. 52, 289-320, (2005).
- [53] Ryan G.J., Jobe L.J., Martin R.: *Symlin*. Clin. Ther. 27 (10), 1500-12 (2005).
- [54] Diabetes in Control Com, News and Information for Medical Professionals Issue #300, (2006).
- [55] FDA accepts Merck's first in class drug application for JANUVIA for type 2. Available at: [www.diabetes@topica.email-publisher.com](http://www.diabetes@topica.email-publisher.com), February 22, (2006).
- [56] Perfetti R., D'Amico E.: *Rational drug design and PPAR agonists*. Curr. Diabetes Rep. 5, 340-345 (2005).
- [57] Nielsen L.L.: *Incretin mimetics and DPP-IV inhibitors for the treatment of type 2 diabetes*. D.D.T, 10, 703-710, (2005).
- [58] Sarabu R., Grimsby J.: *Targeting glucokinase activation for the treatment of type 2 diabetes—a status review*. Curr. Opin. Drug. Discov. Devel. 8, 631-637 (2005).
- [59] Campbell R.K., Campbell L.K., White J.R.: *Insulin lispro: its role in the treatment of diabetes mellitus*. Ann. Pharmacother. 30, 1263-71, (1996).
- [60] Galloway J.A.: *New directions in drug development: mixtures, analogues, and modeling*. Diabetes Care 16(3), S16-S23, (1993).
- [61] Howey D.C., Bowsher R.R., Brunelle R.L., Woodworth J.R.: *[Lys(B28), Pro(B29)]-human insulin, A*

- rapidly absorbed analogue of human insulin. Diabetes* 43, 396-402, (1994).
- [62] Torlone E., Fanelli C., Rambotti A.M., Kassi G., Modarelli F., Di Vincenzo A.: *Pharmacokinetics, pharmacodynamics and glucose counterregulation following subcutaneous injection of the monomeric insulin analogue [Lys(B28), Pro(B29)] in IDDM. Diabetologia* 37, 713-20, (1994).
- [63] Johnson M.D., White J.R., Campbell R.K.: *Insulin therapy in the era of insulin analogs. U.S. Pharmacist* 21, HS35-HS44, (1996).
- [64] Schubert-Zsilavec M., Wurglics M.: *Better blood sugar control in diabetics, Insulin glargin--a long-acting insulin analogue. Pharm. Unserer. Zeit.* 30(2), 125-30, (2001).
- [65] Porcellati F., Rossetti P., Pampanelli S., Fanelli C.G., Torlone E., Scionti L., Perriello G., Bolli G.B.: *Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. Diabet. Med.* (21)11, 1213-1220, (2004).
- [66] Efendic S., Portwood N.: *Overview of incretin hormones. Horm. Metab. Res.* 36, 742-746, (2004).