ABSTRACT

Obesity is well established as a major contributor to the growing prevalence of diabetes, but age is also a factor. Use of multiple agents is often needed to achieve treatment goals. This article reviews non-insulin treatment options in terms of overall safety and efficacy. Insulin resistance is also discussed.


When I first began medical practice in 1991, the prevalence of people diagnosed with diabetes was 4.9%. Just 10 years later, that prevalence has increased by as much as 61%.

Today, 23.6 million people—7.8% of the population—are believed to have diabetes. Approximately 90% to 95% have type 2 diabetes mellitus (T2DM). Obesity is well established as a major contributor to the growing prevalence of diabetes. A lesser known association, however, is that of age. Nearly 25% of people aged 60 and older are believed to have diabetes. Certain ethnic minorities are at greatest risk, such as native Americans, blacks, and Hispanic/Latino Americans.

As pharmacists evolve toward becoming more patient oriented than product oriented, handling the complex needs of this growing population is becoming increasingly important to pharmacy practice. Effective management of diabetes is essential to offset its well-known chronic complications—microvascular, macrovascular, and neuropathic disorders. Figure 1, based on Diabetes Control and Complications Trial data, shows that relative risk for microvascular complications, such as diabetic retinopathy, nephropathy, neuropathy, and microalbuminuria, increases with increasing levels of glycosylated hemoglobin ($A_1C$).

It is important to note that the risk gradient is continuous with no glycemic threshold for developing complications. Although many of these health problems can be prevented or delayed with effective diabetes management, unfortunately, glycemic control is rarely optimal. Definitions of target glycemic control differ across guidelines. Whereas the American Diabetes Association recommends an $A_1C$ target of less than 7%, the American Association of Clinical Endocrinologists sets a more ambitious goal of 6.5% or lower. Treatment options for approaching or achieving these targets are described in the following sections.

TREATMENT OPTIONS

Use of multiple agents is often required to achieve recommended glycemic targets in people with diabetes. Therefore, there is a growing trend toward the use of insulin in combination with oral medication (Figure 2), a therapeutic practice that was all but unheard of when I began my medical practice. At that time there were very few treatment options—insulin and perhaps 2 or 3 oral agents. Today, we have many more options. Available agents target different sites of action. Thiazolidinedione and metformin reduce excessive hepatic glucose output as well as peripheral insulin resistance; absorption inhibitors (acarbose and miglitol) delay carbohydrate absorption in the gas-
**PROCEEDINGS**

**Figure 1. Relationship of A1c to Risk of Complications**

![Graph showing the relationship of A1c to risk of complications](image)

\[ A_{1c} = \text{glycosylated hemoglobin.} \]


**Figure 2. Treatment with Insulin or Oral Medication Among Adults with Diagnosed Diabetes, United States, 2004–2006**

![Pie chart showing treatment with insulin or oral medication](image)


**SIDE EFFECTS AND CONTRAINDICATIONS OF TRADITIONAL ORAL AGENTS**

**SECRETAGOGUES**

Among the first oral medicines available to treat T2DM, the sulfonylureas lower blood sugar by stimulating \( \beta \) cells to make more insulin and are therefore dependent upon a functional pancreas. The long-acting secretagogues are glipizide, glyburide, and glimepiride, whereas short-acting agents in this class include repaglinide and nateglinide. Side effects include weight gain of approximately 2 to 4 kg which is problematic given the association between overweight and diabetes. These agents, glyburide in particular, have been reported to induce hypoglycemia in approximately 1% to 2% of patients. Because sulfonylureas must be titrated once weekly until the most effective dose is achieved, glucose remains largely uncontrolled over this period. Sulfonylureas are contraindicated in people with sulfita allergies.

**METFORMIN**

This drug is an insulin sensitizer that decreases hepatic glucose production and increases peripheral glucose uptake and utilization. Unlike sulfonylureas,
metformin generally does not produce hypoglycemia. It is contraindicated in patients with certain levels of renal insufficiency and in patients administered intravenous (IV) contrast within 48 hours, while the diagnosis of congestive heart failure carries with it significant caution with metformin use. Lactic acidosis is a rare, but serious, metabolic complication that can occur. Common side effects include diarrhea (53%) and nausea and vomiting (26%). Clinicians should be mindful of the potential for B12 deficiency in metformin-treated patients.

**Thiazolidinediones**

Thiazolidinediones (TZDs; rosiglitazone and pioglitazone) are also insulin sensitizers but the site of action is predominantly muscle and fat. TZDs can exacerbate congestive heart failure in some patients and are not recommended in patients with symptomatic heart failure. They are contraindicated in patients with class III or IV heart failure and in patients with significant hepatic impairment. Dose-related edema, weight gain, and anemia (probably due to hemodilution) may occur. A known limitation of TZDs is that maximum therapeutic efficacy can take up to 12 weeks.

**Incretin System Modifiers**

In recent years, an improved understanding of the incretin effect on the pathophysiology of T2DM has led to development of new treatments. This effect is in part a function of glucagon-like peptide-1 (GLP-1), which is secreted from the intestinal L cells upon the ingestion of food and is believed to enhance the secretion of insulin. GLP-1 appears to be diminished in people with T2DM, and may therefore partially account for reduced insulin secretion in this population.

The incretin effect was first observed in a novel study that demonstrated that physiological responses to glucose varied when glucose was administered orally versus when it was administered intravenously. Specifically, the increasing plasma glucose resulting from ingestion of 50 g oral glucose resulted in an increase of C-peptide, a measure of insulin secretion. An isoglycemic IV glucose infusion designed to mimic the plasma glucose excursion achieved by the oral glucose load was later administered to the same study patients. Despite the same plasma glucose profiles, significant differences were observed in the B-cell response, as measured by C-peptide. Integrated C-peptide responses were 1.3-, 2.3-, and 3.6-fold greater after oral glucose loads of 25, 50, and 100 g, respectively, compared to the values in the respective isoglycemic IV infusion experiments (P <.05 for all glucose loads). This incretin effect suggested that incretins, and not merely the direct actions of plasma glucose, affect the insulin secretory response. When additional research showed the incretin effect to be impaired in people with T2DM, incretin-based therapies were seen as having the potential to impact the path of the disease. In 2005, exenatide, an injectable GLP-1 analogue, was approved by the US Food and Drug Administration. One year later, the oral agent sitagliptin was approved. Sitagliptin inhibits the enzyme DPP-4, which is known to rapidly inactivate GLP-1. Inhibition of DPP-4 extends the half-life of naturally produced GLP-1 to prolong its effects.

Incretins have been shown to be effective in improving all measures of glycemic control—A1C, fasting plasma glucose, and postprandial plasma glucose—with greater reductions in postprandial glycemia than in fasting glycemia. Data support that these agents can be used at any stage of T2DM in drug-naïve patients or as adjunct therapy.

Incretin-based therapy with GLP-1 analogues or DPP-4 inhibitors in T2DM is moderately effective in improving glycemia. The demonstrated efficacy of incretin therapy on postprandial glycemia provides clinicians with additional treatment options that have not been associated with weight gain. GLP-1 analogues have been associated with gastrointestinal side effects (nausea 18%, vomiting 4%, and diarrhea 6%). DPP-4 inhibitor use is associated with stuffy or runny nose, sore throat, headache, diarrhea, upper respiratory infection, joint pain, and urinary tract infection (with differences ranging from 0.1%–1.5% vs placebo). More detailed information about incretin mimetics and DPP-4 inhibitors is presented elsewhere in this monograph.

**Insulin Resistance**

Type 2 diabetes mellitus is a disease of insulin deficiency along with insulin resistance, and the natural history is a progressive worsening of insulin secretion over time. We know clinically that most patients will eventually need insulin therapy. Although historically we have assumed that the primary barrier to insulin use is needle adversity, our experience with GLP-1 analogs suggests that this may in fact be a mispercep-
tion. Adversity to insulin use is often a function of its untoward effects: the potential for weight gain and hypoglycemia. Consequently, many healthcare providers are reluctant to prescribe insulin, and many patients are unwilling to use it. Another problem is many providers are uncertain how to use insulin in T2DM, and can become confused by the variety of insulin preparations that are available and their diverse pharmacokinetic profiles.

Generally, human insulin, which is synthesized by genetically altered microorganisms, has a more rapid onset and a shorter duration of action than previous preparations derived from animal pancreas. Regular human insulin has an onset of action of approximately 30 to 60 minutes, with peak concentrations reached at between 2 to 4 hours while the “intermediate-acting” insulins (eg, NPH) have gradual onset and peak effects usually between 4 to 8 hours and total duration of 10 to 20 hours. Rapid-acting insulin analogs (insulin lispro and glulisine) have desirable action profiles at mealtimes because they have onset of action of 5 to 15 minutes, a peak that occurs 1 hour post-administration, and an insulin effect that practically vanishes 4 hours post-administration. The extended-acting insulin analogs (insulin glargine and detemir) have no pronounced peak, are absorbed within 1 to 2 hours post-administration, and have a plasma concentration approximately 50% lower than that seen with NPH insulin but with twice the duration of action. The complexity of insulin pharmacokinetics and the time needed to adjust dosing regimens occasionally prompts primary care providers to refer patients to an endocrinologist in order to achieve an optimal treatment regimen.

CONCLUSIONS
Although it is important to continue research to determine the long-term safety and efficacy of newer agents, it is also vital that further research be done in the area of pharmacoeconomics. It is possible that with the potential to improve β-cell function, existing or newer agents may possibly slow down or even prevent diabetes progression. This could result in significant cost savings through fewer cases of severe diabetes and reduced long-term complications.

In order to effectively improve diabetes management, pharmacists must adopt an uncompromising “treat to target” approach to care. This involves early pharmacologic interventions and persistent titration of those medications to achieve glycemic control and maintain targets safely.

DISCUSSION

Dr Cross: We have had some discussion about how long the patient has had the disease prior to diagnosis, and the Holy Grail of preventing β-cell apoptosis. If we can make some impact on that as early in our management of patients as possible, we can impact the whole progression of the disease. We may be able to change the entire face of this disease, in much the same way that the progression of HIV has changed dramatically in the past 20 years. Might drugs that target the incretin system become the sulfonylureas of type 2 diabetes in another 5 or 7 years?

Dr Cornell: Yes, saving the β cell is crucial. There may be additional therapeutic options for accomplishing this. For example, there have been several studies of early insulinization in T2DM in newly diagnosed patients who were given insulin pumps for 2 weeks only. Three months later, 72% of these patients had no diabetes, and at 1 year, 42% still had no disease. So our therapeutic strategy involves saving the β cell, helping patients to learn about lifestyle changes, and also helping patients to overcome their fears of insulin. Often patients feel once they go on insulin they have failed everything else and they are doomed. They do not realize that no drug will be the single therapeutic option for the duration of the disease. They can go on insulin. They can go off insulin. They can use oral agents. They can go off of oral agents.

Dr Alvarez: Although much of the epidemiology shows an increase in complications associated with diabetes at a fasting blood glucose of 126 mg/dL or 7 mmol/L, many patients with glucose intolerance or impaired fasting glucose present with these complications. We saw that with the UKPDS (UK Prospective Diabetes Study) entry criteria. UKPDS is a large trial that evaluated more than 5000 newly diagnosed patients with T2DM. Approximately 30% of these newly diagnosed patients with T2DM had diabetic retinopathy. By way of example, a patient in my clinic last week complained of neuropathies, a common complication of diabetes, and her fasting blood glucose was 105 mg/dL. Although this patient does not fit the criteria for the diagnosis of diabetes, she clearly has dysglycemia and complications associated with diabetes. I think this patient could benefit from intervention. Even patients who are at the upper ends of
normal glycemia, with a 2-hour postprandial blood glucose of 115 mg/dL, may already have \( \beta \)-cell dysfunction.\(^2\) That is why I think the diagnosis is pretty arbitrary, and I think we need to look at this as a whole spectrum, not necessarily as numerical cutoffs.

**Dr Rodgers:** Clinically, it is very difficult to identify prediabetes cases. These patients are presenting with hypertension. I agree there is definite value in early intervention, and it can even be cost effective, but getting a community provider to identify patients early in the disease course is challenging.

**Dr Rich:** I would be very interested in understanding the psychology of a patient who is willing to receive an injectable GLP-1 analog, but resists insulin injection. That intrigues me, knowing that insulin will likely be much more effective in reducing A1c.

**Dr Alvarez:** The answer that you will get from patients is, “my relative was put on insulin and died shortly thereafter or developed a complication associated with diabetes.” The patient immediately places the blame on insulin for these untoward events.

**Dr Rich:** I think that represents a failure in the medical system that people view insulin as the last resort.

**Dr Cornell:** That is because we have an acute care health system. We wait until a problem happens and then we try to fix it. We are putting Band-Aids on hemorrhages. What we need to do is prevent the problem from happening, to change the dynamic to a preventive care model.

**Dr Elasy:** There is no question that if you treat prediabetes, good things happen. If you look at the Diabetes Prevention Program study,\(^3\) some of the patients with prediabetes actually regressed. I think it is not an open question that treating them is salutary as it relates to prevention in diabetes. It is just a question of how much and what to use. More research is needed. I typically put these patients on metformin and recommend diet and exercise.

**Dr Rich:** What is needed is a new paradigm of educating the patient about exercise and diet, and convincing payers of the value in reimbursing for diabetes education.

**Dr Cornell:** Ideally, there would be a diabetes educator on staff at every primary care office so that the problem is not progressing to the train wreck we see showing up in the endocrinologist’s office 10 to 14 years after disease onset. Let us get aggressive early on. I do think the incretins have a role because they impact 4 out of the 5 broken organs: the pancreas, the gastrointestinal tract, the liver, and the brain.

**Dr Cross:** So is one of the most important questions, then, how long have you had diabetes? Is that what we should be asking the first time we meet our patient?

**Dr Elasy:** Absolutely. But there is some controversy in terms of duration of disease and the extent of \( \beta \)-cell dysfunction. And there are no comparative data across treatments with an end point of \( \beta \)-cell dysfunction. But I do think duration of the disease should inform the treatment decision. Is the answer a functional assessment of \( \beta \)-cell function or do we use disease duration as a proxy for \( \beta \)-cell assessment? I think the latter is more practical, but of course not as precise.

**Dr Cross:** What is needed is an easy test, such as a point-of-care test, to determine the patient’s ability to utilize glucose in the periphery and to assess \( \beta \)-cell function. That would enable us to do a lot more fine-tuning of treatment early on. That is perhaps something we can look forward to in the future.

### REFERENCES


