Type 2 Diabetes: Limitations of Current Therapies

ABSTRACT: Type 2 diabetes is a chronic disease associated with numerous microvascular and macrovascular complications. It affects millions of persons worldwide, posing an enormous socioeconomic burden. A growing body of evidence shows that comorbidities are greatly reduced when adequate glycemic control is achieved. Unfortunately, despite the variety of therapies currently available, the majority of patients do not achieve glycemic goals. Recent evidence demonstrating that diabetes progression can be stopped or even reversed with early and aggressive intervention, and the advent of therapies that address several of the mechanisms of diabetes pathophysiology, offers much promise for the future. This review article will identify the direct and indirect limitations of current type 2 diabetes therapies, and will explore new ways in which these limitations can be overcome.

The prevalence of type 2 diabetes is relentlessly increasing as a result of today’s more sedentary lifestyles and increased obesity. In 2000, an estimated 171 million people worldwide had diabetes, and the number is projected to reach 366 million by 2030, resulting in high morbidity and a large economic burden.

The pathophysiology of type 2 diabetes is progressive, characterized by decreased insulin sensitivity, deteriorating β-cell function, and decreased incretin function. Decreased insulin function leads to chronic hyperglycemia (during fasting and postprandial periods) and acute glycemic fluctuations. These may be associated with microvascular and macrovascular complications caused by excessive protein glycation and activation of oxidative stress. The ultimate goal of type 2 diabetes treatment, therefore, should be to reduce all the components of dysglycemia.

CAN DISEASE PROGRESSION BE HALTED?

Type 2 diabetes is typically managed with rigorous medical therapy and a stepwise approach, including initial lifestyle modifications, the addition of oral antidiabetic drugs (OADs), and the addition of insulin. Fortunately, early educational intervention can halt or even reverse disease progression. For example, Tuomilehto and colleagues and the Diabetes Prevention Program Research Group investigated the effect of intensive nutrition and exercise counseling on the progression from impaired glucose tolerance (IGT) to type 2 diabetes. A 58% relative reduction in the progression to diabetes was observed in both studies compared with standard diet and exercise programs.

Programs that promote a healthier diet and more active lifestyle can be very successful in helping patients achieve weight loss in the short term. Patients enrolled in such programs lose approximately 10% of their body weight over 20 to 26 weeks, which can provide significant reductions in hemoglobin A1c (HbA1c) levels (about 1% to 2%) and improvement in cardiovascular disease risk factors. Unfor-
Unfortunately, this approach alone fails to achieve adequate glycemic control within 1 year for the majority of patients. It is extremely difficult for patients to modify lifelong habits, and most will ultimately require pharmacotherapy to restore normoglycemia. Despite the potential of lifestyle modifications and early intervention to halt disease progression, the majority of patients currently have poor glycemic control, with less than 50% reaching the recommended American Diabetes Association (ADA) target of HbA1c levels lower than 7%.8,9

**CAN THERAPEUTIC LIMITATIONS BE OVERCOME?**

OADs are normally introduced when lifestyle modifications fail to adequately control glycemia. They are very useful for managing hyperglycemia, especially in the early stages of disease, achieving typical HbA1c reductions of 0.5% to 2.0%.10 However, there are several limitations that prevent OADs from reaching their potential.

**Direct limitations: mechanisms of action and side effects.** The success of OADs is limited by their mechanisms of action, which often address the symptoms of diabetes rather than its underlying pathophysiology. OADs may also have undesirable side effects. For instance, up to 2.5% and 17.5% of sulfonylurea (SU)-treated patients experience major and minor hypoglycemia, respectively, while GI problems affect up to 63% of metformin, 36% of thiazolidinedione (TZD)-, and 30% of acarbose-treated patients. Peripheral edema is observed in up to 26% of TZD-treated patients, and body weight increases of 2.2 to 11.0 lb (1 to 5 kg) are common with both SU and TZD therapy.11 These side effects can have a negative impact on patient adherence to treatment, resulting in higher HbA1c levels and increased risk for all-cause hospitalization and all-cause mortality.12

**Overcoming limitations: failure of sufficiently proactive disease management.** Another limitation hindering the efficacy of OADs is clinical inertia on the part of health care practitioners who delay initiation and intensification of therapy. OADs are frequently initiated too late in the progression of the disease and intensification is delayed, needlessly exposing the patient to damaging levels of hyperglycemia. For example, a retrospective observational study showed that patients with type 2 diabetes received monotherapy with metformin or an SU for 14.5 and 20.5 months, respectively, before additional treat-
ment was initiated, in spite of HbA1c levels higher than 8%. This is much later than recommended in the most recent American Association of Clinical Endocrinologists (AACE) road map guidelines, in which combination therapy is indicated when continuous titration of OAD monotherapy fails to achieve target HbA1c levels (ie, ≤ 6.5%). Although insulin is the most effective antihyperglycemic agent, its initiation is also delayed to an excessive degree. Brown and associates estimated that the average patient accumulated almost 5 HbA1c years of excess glycemic burden (HbA1c > 8%) from diagnosis until insulin initiation, increasing the prevalence of complications.

Clinical inertia has a negative effect on the economic burden of diabetes as well, since the direct costs of the disease increase greatly as complications develop. Therefore, there is a growing consensus that a more aggressive approach to diabetes management must be implemented. This approach involves prompt intensification of OADs as soon as they fail to achieve HbA1c targets, and earlier initiation of combination therapy, since adding an OAD with a complementary mechanism of action can have an additive or synergistic effect on glucose control. For example, SU and metformin combination therapy has been shown to reduce HbA1c levels by 1.7% in patients who were not achieving adequate glycemic control with SU monotherapy, and where increases in SU dose or switching to metformin monotherapy did not significantly reduce HbA1c levels. Unfortunately, OADs are unable to mitigate the inevitable and progressive β-cell decline that occurs during the natural progression of diabetes. Even if treatment is intensified promptly, 50% of patients who have had a diagnosis of type 2 diabetes for more than 10 years and 75% who have had a diagnosis for at least 20 years do not achieve adequate glycemic control with OAD therapy alone.

**INSULIN: LIMITATIONS AND SOLUTIONS**

Currently, insulin therapy is the only medication with the proven potential to bring any patient to glycemic target at any point in the progression of the disease. It is typically prescribed after OADs have failed, and regretfully often later than is ideal. Glucose is the main stimulator of insulin secretion, and glucose levels in healthy individuals are maintained within relatively narrow limits. The physiological plasma insulin profile in healthy individuals displays low but constant insulin levels in fasting conditions, with sharp prandial peaks shortly (within 30 minutes) after meals followed by a slow return to basal levels when increased insulin secretion is no longer necessary. In order to avoid glycemic excursions, exogenously administered insulin would ideally closely mimic the healthy physiological pharmacokinetic insulin profile.

**Direct limitations.** Unfortunately, conventional human insulin is associated with several characteristics that limit its potential. Unmodified human insulin injected intravenously has a 17-minute half-life and a short duration of action. However, when subcutaneously injected for mealtime control, human insulin has a slower onset of action and a prolonged effect compared with endogenous insulin, but must be injected 30 to 60 minutes before the meal in order to avoid postprandial hyperglycemia and between-meal hypoglycemia.

Intermediate-acting human insulin (ie, neutral protamine hagedorn [NPH]) used for basal glucose control has pronounced nonphysiological peaks in serum concentration 4 to 8 hours after injection. This failure to mimic the physiological insulin profile often results in a mismatch between blood glucose and insulin peaks, predisposing the patient to hypoglycemia. Nocturnal hypoglycemia is of particular concern, since patients are unlikely to recognize the warning symptoms or wake up during an event and are thus unlikely to take any preventative action.

Two randomized trials comparing NPH insulin with the insulin analogs insulin detemir and insulin glargine, respectively, have highlighted the higher incidence of overall and nocturnal hypoglycemia associated with the nonphysiological profile of human insulins. Currently, insulin therapy is the most effective antihyperglycemic agent, its initiation is also delayed to an excessive degree. Brown and associates estimated that the average patient accumulated almost 5 HbA1c years of excess glycemic burden (HbA1c > 8%) from diagnosis until insulin initiation, increasing the prevalence of complications.

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is associated in some cases with needle aversion, social stigma, lack of convenience, difficulty with accurate dosing and, eventually, decreased adherence to the prescribed insulin regimen.28 Up to 25% of patients experience anxiety about self-injection, and discrepancies between the intended dose and the dose that is actually delivered can be greater than 25% in many patients.29 Another important limitation of vial and syringe administration of insulin is the risk of needlestick injury among health care providers. In a retrospective study of nurses caring for patients with diabetes, 80% of all reported needlestick injuries were caused by disposable syringes.30

**Indirect limitations.** The limitations of conventional insulin therapy have given rise to a number of barriers to timely initiation and intensification, including physicians’ unwillingness to prescribe insulin and patients’ nonacceptance of insulin therapy, resulting in unnecessary exposure of the patient to hyperglycemia.17 These issues are described in greater detail in a separate article on clinical inertia in this supplement (page S20).

**Overcoming barriers to appropriate insulin use.** Many patients are able to reach and sustain glycemic goals with aggressive and continual insulin dose titration,21 and there is a growing call for earlier and more aggressive intensification of insulin as a result. For example, the most recent guidelines issued by the AACE25 call for therapy-naive patients with HbA1c levels higher than 10% to initiate insulin with either basal-bolus therapy or premixed insulin. The same approach was recommended for OAD-treated patients with HbA1c levels remaining higher than 8.5%.16 The benefits associated with newer insulin analogs (vs conventional insulin) and newer insulin pen delivery devices (vs vial and syringe) may facilitate implementation of these guidelines by reducing barriers to insulin initiation and intensification.

**New insulin analogs and delivery systems.** Numerous studies have shown that the new analogs, which have improved pharmacokinetic and pharmacodynamic profiles (Table 1), are effective in reducing HbA1c levels with a lower risk of overall and nocturnal hypoglycemia compared with conventional insulins,21,22 Insulin detemir has also been shown to consistently reduce within-subject variability in plasma glucose levels compared with NPH insulin in type 2 diabetes patients on basal-bolus therapy,33 and this has been strongly associated with a reduced incidence of nocturnal hypoglycemia in the clinical setting.

Three-month data from the global prospective multinational observational PREDICTIVE study, which follows patients with type 1 and type 2 diabetes who were treated with NPH insulin or insulin glargine prior to the study and switched to insulin detemir, showed that after switching, the percentage of patients with type 2 diabetes who experienced nocturnal hypoglycemia decreased from 13.4% to 2.8% (P<.001) in association with reduced plasma glucose variability (reduced from 15.7% to 12.9% [P<.01]; r = 0.145; P<.001).34 Reduced glycemic variability could also have a beneficial effect on diabetes complications, since glycemic variability has been shown to contribute to oxidative stress by increasing superoxide production (which itself has been implicated in many of the hyperglycemia-induced mechanisms involved in the development of diabetes complications).35,36

Insulin detemir has also been shown to induce less weight gain than either NPH or insulin glargine.24 In a 26-week study comparing the effect of twice-daily insulin detemir versus twice-daily NPH insulin as add-on therapy to OADs in insulin-naive patients with type 2 diabetes, weight increases of 2.6 lb (1.2 kg) versus 6.16 lb (2.8 kg), respectively, were observed.21 Similarly, in a 52-week study comparing once-daily detemir versus once-daily glargine as add-on therapy to OADs in insulin-naive patients, weight increases of 5.1 lb (2.3 kg) versus 8.6 lb (3.9 kg), respectively, were reported.37

Modern pen devices for insulin delivery are easy to use, cause little or no pain, and are preferred by patients over vial and syringe,38,39 all of which are likely to have a positive effect on patients’ adherence to insulin therapy.40 Studies comparing the dosing of basal insulin in patients with type 2 diabetes using different delivery systems have shown that insulin detemir dosing once-daily versus twice-daily is associated with a reduced incidence of nocturnal hypoglycemia in the clinical setting.
ing accuracy of pen devices versus vial and syringe have shown pens to be more accurate, particularly for the elderly and for patients delivering low insulin doses.39 Some modern pen devices such as the NovoFine® Auto-cover® (Novo Nordisk) 30 gauge × 1/3-in (8-mm) (NFA) needle, a single-use product with an automatic safety lock, and the BD Autoshield™ Pen Needle (Becton-Dickinson), which has a shield that locks in place after injection, have been designed specifically to minimize the risk of needlestick injury.41

PATIENT EDUCATION AND DIABETES MANAGEMENT PROGRAMS

Patient education plays an important role in reducing barriers to lifestyle modifications and initiating or intensifying treatment. This can maximize the potential for improved glycemic control. It is important to stress the progressive nature of diabetes to patients at the time of diagnosis, as well as the fact that insulin may eventually be needed to achieve good glycemic control and avoid complications.28

Structured intensive diabetes education programs (SIDEPs) can motivate and empower patients to take control of their disease and have been associated with improved glycemic control, increased adherence to treatment, and improved acceptance of insulin.

In a study of patients with type 2 diabetes who underwent an in-patient SIDEP versus hospitalized patients aiming for glycemic control without intensive education, the group receiving intensive education had significantly improved HbA1c levels, less frequent subsequent hospitalizations, and improved adherence to self-care behavior.42

Project Dulce also demonstrated the efficacy of nurse care management and peer education and empowerment groups in the treatment of patients with diabetes in underserved ethnic populations. Patients enrolled in the project were primarily Latino, and all had diagnosed type 1 or type 2 diabetes. After 1 year, HbA1c levels, total cholesterol, LDL cholesterol, and diastolic blood pressure were significantly lower in the enrolled subjects than in a matched control group. Standards of diabetes care, knowledge of diabetes, treatment satisfaction, and culture-based beliefs were also improved.43 These studies highlight the importance of optimum patient management and education in achieving adequate glycemic control in a clinical setting.

THE PROMISE OF INCRETIN-BASED THERAPIES

The incretin hormones glucagon-like peptide-1 (GLP-1) and glucagon-dependent insulin-releasing polypeptide (GIP) are released in the intestine shortly after nutrient ingestion; they are responsible for mediating the “incretin effect” (ie, the enhanced insulinotropic effect observed after oral glucose administration compared with an isoglycemic intravenous challenge)44 by inducing glucose-dependent insulin secretion. In persons with type 2 diabetes, however, there is a marked decrease in the insulinotropic effect of GIP,46,47 together with probable decreased secretion of GLP-1,46,47 which may contribute to the deficient postprandial insulin response observed in this disease.48

A new generation of therapies aimed at enhancing incretin action in type 2 diabetes is currently being developed, including agents that inhibit the dipeptidyl peptidase-4 (DPP-4) enzyme responsible for rapid degradation of GLP-1 (DPP-4 inhibitors: sitagliptin, alogliptin, and saxagliptin), as well as agents that are able to bind to and activate GLP-1 receptors while remaining less susceptible to DPP-4 degradation than native GLP-1 (GLP-1 receptor agonists such as exenatide and human GLP-1 analogs such as liraglutide). Exenatide is derived from a peptide found in the saliva of Heloderma suspectum (also known as the Gila monster). It shares only 53% of its structure with native GLP-1 and is therefore less susceptible to DPP-4 degradation than the native molecule; however, because of the lower sequence identity to human GLP-1, exenatide elicits antibody formation in about 43% of patients.50 The clinical significance of this remains unclear.

Liraglutide, on the other hand, is a fully human protein and shares 97% of its sequence with native GLP-1, with a single amino acid substitution and the addition of an acyl side chain responsible, in part, for its extended half-life.50 Antibody formation with liraglutide occurs in up to 12.7% of patients.51

Unlike the majority of traditional treatment options, incretin-based therapies address several of the mechanisms that contribute to type 2 diabetes by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner, thus reducing the risk of hypoglycemia. These agents also reduce plasma glucose levels, sometimes with clinically meaningful associated weight loss (in the case of exenatide and liraglutide) or without weight gain (in the case of DPP-4 inhibitors) (Table 2). Exenatide and liraglutide have the additional advantage of improving biomarkers of β-cell function.50

Limitations of GLP-1 receptor agonists are the associated GI side effects that typically occur at treatment inception. In particular, nausea has been reported in 40% to 50% of patients receiving exenatide 5 or 10 µg twice daily,50 and in 7% to 40% of patients receiving liraglutide 0.6, 1.2, or 1.8 mg once daily.51,53,56 Nausea ap
pears to be transient, in most cases occurring only during the first 1 to 2 weeks of treatment. Thus, these therapeutic agents are a promising new option for the management of type 2 diabetes that can be used as first-line monotherapy and in combination with 1 or more OADs. The ADA, AACE, and European Association for the Study of Diabetes recognize the value of incretin-based therapies, and recommend their initiation when lifestyle modification and metformin are insufficient to lower HbA1c to below 7%.7

CONCLUSION
Although type 2 diabetes is a progressive disease, evidence shows that early educational and pharmacological intervention can stop or even reverse its progression. Despite this, diabetes in the majority of patients is poorly controlled, which increases the burden of comorbidity and the cost of disease management. This failure to achieve optimum glycemic control partly results from the limitations of current therapies, which in most cases target the symptoms of the disease but not its underlying causes. Still, a more diligent approach to disease management involving patient education and aggressive intensification of treatment, through combination therapy and timely use of insulin when needed, can control disease. In addition, emerging treatments such as the incretin-based therapies offer the promise of even better glycemic control through mechanisms of action that tackle the disease pathophysiology, not just its symptoms.

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