Improving Care for Patients With Type 2 Diabetes: Applying Management Guidelines and Algorithms, and a Review of New Evidence for Incretin Agents and Lifestyle Intervention

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Abstract

Diabetes affects an estimated 25.8 million US adults, or 8.3% of the population. By 2050, the prevalence of type 2 diabetes mellitus (T2DM) in the United States may be as high as 1 in 3 adults. This paper summarizes key national treatment goals, guidelines, and algorithms for T2DM management in a way that clarifies their similarities and areas of disparity, for use by managed care organizations and other healthcare professionals. In addition, the role of long-standing and newer classes of antihyperglycemic agents, including incretin-related agents, bromocriptine, and colesevelam, will be reviewed, as will emerging research on the role of lifestyle intervention in T2DM and prediabetes. Lastly, comparative and long-term clinical efficacy data on incretin therapy, reported at the American Diabetes Association's 2011 71st Scientific Sessions, will be summarized. Although the treatment landscape for T2DM has increased substantially in complexity, major guidelines have similar goals. While established, relatively inexpensive, and thoroughly investigated antihyperglycemic agents maintain popularity, incretin-based agents offer glycemic efficacy along with other benefits relative to weight loss or neutrality and low rates of hypoglycemia. In addition, the feasibility of matching patients to appropriate lifestyle intervention, for both diabetes and diabetes prevention, is increasing.

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For author information and disclosures, see end of text.

Diabetes affects an estimated 25.8 million US adults, or 8.3% of the population.[1] By 2050, the US Centers for Disease Control and Prevention (CDC) estimates the prevalence of type 2 diabetes mellitus (T2DM) in the United States may be as high as 1 in 3 adults.[2] Diabetes is the leading cause of adult blindness and end-stage kidney disease. It increases the risk for cardiovascular (CV) disease by 2- to 4-fold, and is the seventh leading cause of death for Americans.[1] In 2007, total US medical costs attributable to diagnosed and undiagnosed diabetes were estimated at $174 billion; of this, $116 billion was spent on medical care and $58 billion was lost due to reduced productivity.[3]

This paper will summarize some key national treatment goals, and guidelines and algorithms for the management of T2DM that may be incorporated by managed care organizations into their internal T2DM treatment protocols. The role of some newer classes of antihyperglycemic agents, especially incretin-related agents, will be reviewed, as will some new clinical data reported at the American Diabetes Association's (ADA's) 71st Scientific Sessions (June 24-28, 2011; San Diego, CA). This paper will also discuss some emerging research on the role of lifestyle intervention in T2DM.

Type 2 Diabetes Pathophysiology and Therapeutics

In most patients who develop T2DM, peripheral insulin resistance in muscle and fat cells develops, along with insulin resistance in the liver. Initially, pancreatic beta-cells are able to compensate for this decreased insulin sensitivity via increased insulin production. Eventually, however, beta-cells fail to fully counteract insulin resistance, leading to the inability to maintain normal glucose homeostasis.[4] In clinical practice, the relative contributions of beta-cell dysfunction and decreased beta-cell mass and insulin resistance to an individual patient's hyperglycemia will vary based on a number of factors, such as patient ethnicity, age, duration of disease, and physical activity and lifestyle habits. Diabetes does not develop, however, without at least a relative insulin secretory deficiency.[5]

Another contributor to the pathogenesis of T2DM is impairment of the postprandial insulin response, mediated by the

incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). In healthy, nondiabetic individuals, release of these hormones in response to oral intake is responsible for an estimated 70% of postprandial insulin secretion; in addition, at least in animals, data indicate that both GLP-1 and GIP promote beta-cell growth and prevent apoptosis. GLP-1 inhibits the secretion of glucagon by pancreatic alpha-cells, thus inhibiting the postprandial release of hepatic glucose; it also promotes the secretion of insulin in response to increasing plasma glucose, as does GIP. In T2DM, the insulinotropic effects of GIP are inhibited. While some studies indicate that diabetes-related diminished postprandial insulin secretion and glucagon suppression are due to a decrease in GLP-1 secretion, other research suggests that there is a decreased effect of GLP-1 which can be at least partially overcome by administering larger amounts of exogenous GLP-1 or increasing endogenous GLP-1 levels.[6]

Established T2DM antihyperglycemic medications have a strong, long-standing evidence base demonstrating their ability to address 1 or more of these core defects. The most commonly used drugs in T2DM are the biguanide metformin, sulfonylureas, thiazolidinediones (TZDs), and exogenous insulin therapy. The most commonly used newer therapies are the incretin-related agents (consisting of GLP-1 receptor agonists and dipeptidyl-peptidase-4 [DPP-4] inhibitors). **Table 1** provides a summary of most available T2DM drug classes, developed by a writing group assembled by the American Association of Clinical Endocrinologists (AACE); treatments are classified based on their effects on fasting and postprandial glucose, as well as associated adverse effects.[7]

Metformin has a substantial beneficial effect on glycosylated hemoglobin (A1C) levels and can be associated with modest weight loss and favorable lipid reductions.[8] However, metformin does not appear to exert any protective effect on beta-cells.[4] Sulfonylureas have a potent initial A1C-lowering effect, but are associated with weight gain and relatively high rates of at least minor hypoglycemia.[4,8,9] These drugs are now also recognized to often have a limited durability of antihyperglycemic efficacy.[4,9] The TZDs contribute to improved insulin sensitivity (even in low doses) and may help to preserve beta-cell function.[4] Recently, however, TZDs have been associated with risks for certain adverse events, including weight gain, edema, congestive heart failure, bone fracture, bladder cancer, and possible ischemic heart disease (rosiglitazone).[8-10] Insulin is the most effective glucose-lowering agent available. Compared with multiple oral agent use, the earlier initiation of insulin may allow patients to achieve more rapid and/or better glycemic control. Insulin can also improve dyslipidemia, but may be associated with weight gain and hypoglycemia.[11,12]

In recent years, our understanding of T2DM pathophysiology in the gut, as well as the liver, kidney, pancreas, and brain, has broadened.[4] Two classes of incretin-related therapies are available: GLP-1 receptor agonists and DPP-4 inhibitors.[13] GLP-1 receptor agonists bind to GLP-1 receptors in the pancreas to stimulate pancreatic insulin release and suppress glucagon, both in a glucose-dependent manner. The drugs' glucose dependency reduces the risk for hypoglycemia. They also have effects on gastric emptying and satiety.[11] GLP-1 receptor agonists are associated with substantial (0.8%-1.2%) improvements in A1C levels, reductions in weight and blood pressure levels, and evidence of improved beta-cell function.[4,14,15] The DPP-4 inhibitors impede the function of DPP-4, the gut enzyme responsible for rapid degeneration of endogenous GLP-1 and GIP.[6] These agents result in a 2- to 3-fold increase in endogenous levels of GLP-1, which results in a glucose-dependent increase in insulin secretion and suppression of glucagon secretion.[11,16] DPP-4 inhibitors do not slow gastric emptying or have a significant effect on satiety, but are associated with improvements in A1C levels (0.5%-0.8%), weight neutrality, and there is some evidence of association with improved beta-cell function.[11,17]

Two additional more recently approved therapies for T2DM management are worth noting. Colesevelam is a bile acid sequestrant developed as a lipid-lowering agent; it also has blood glucose–lowering properties and was approved by the US Food and Drug Administration (FDA) in 2008 to treat hyperglycemia associated with T2DM. Colesevelam is weight neutral, and in clinical trials, the risk for hypoglycemia was similar to placebo.[18] Quick-release bromocriptine is a sympatholytic D2 dopamine agonist recently approved for T2DM, with a low risk for hypoglycemia or weight gain. In addition to lowering A1C levels, quick-release bromocriptine reduces free fatty acid and triglyceride levels. Quick-release bromocriptine is the first agent to successfully complete the FDA-mandated cardiovascular safety trials for new antihyperglycemic medications; these trials found that the incidence of a composite cardiovascular end point was not increased with bromocriptine relative to placebo. In fact, the hazard ratio comparing quick-release bromocriptine to placebo for the time to first occurrence of the end point was 0.58 (0.35-0.96).[4,19]

Treatment Goals and Therapeutic Strategies

Despite some variance, current guidelines for blood glucose management in T2DM are more similar than they are different. For example, and as shown in **Table 2**, the ADA

■ **Table 1.** American Association of Clinical Endocrinologists' Summary of Key Benefits and Risks of T2DM Medications[7]

SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

	MEDICATIONS*									
	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

The term 'glinide' includes both repaglinide and nateglinide.
CHF indicates congestive heart failure; DPP4, dipeptidyl-peptidase-4; GLP-1, glucagon-like peptide 1; T2DM, type 2 diabetes mellitus.
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recommends an A1C goal of less than 7% for most patients, with preprandial plasma glucose goals of 70 to 130 mg/dL and a peak postprandial plasma glucose goal of less than 180 mg/dL.[20] The AACE recommends an A1C goal of 6.5% or less, with preprandial plasma glucose less than 110 mg/dL, and 2-hour postprandial plasma glucose less than 140 mg/dL.[16]

Both organizations emphasize the need to individualize glycemic goals based on a number of patient-specific characteristics. These include the duration of diabetes, patient age, life expectancy, ethnicity, the presence of microvascular and macrovascular complications, other comorbid illnesses, CV risk factors, hypoglycemia unawareness, and patient risk for severe hypoglycemia.[7,16,20] The ADA notes that lower A1C goals (if they can be achieved without hypoglycemia or other adverse effects) may be targeted in subjects with a short duration of diabetes, long life expectancy, no significant CV disease, and no significant hypoglycemia. In contrast, A1C targets should be less stringent in certain individuals, including those with a history of frequent or severe hypoglycemia or hypoglycemic unawareness, advanced vascular complications, and/or extensive comorbidities, as well as those with long-standing T2DM in whom lower A1C goals may be difficult to achieve despite optimal treatment.[21]

Expert groups assembled by the ADA (in collaboration with the European Association for the Study of Diabetes [EASD]) and by the AACE (in collaboration with the American College of Endocrinology [ACE]) have also developed T2DM treatment algorithms. While not official position statements, the goal of these algorithms is to identify and describe strategies to better utilize presently available antihyperglycemic agents. However, both algorithms emphasize the importance of lifestyle interventions (medical nutrition therapy and appropri-

Table 2. 2011 AACE/ACE and ADA Glycemic Control Recommendations for T2DM[16,20]

Target Treatment Goals	AACE/ACE	ADA
A1C level	≤6.5%	<7.0%
Fasting glucose	Fasting plasma glucose: <110 mg/dL	Preprandial capillary plasma glucose: 70-130 mg/dL
Postprandial glucose	2-hr postprandial glucose: <140 mg/dL	Peak postprandial capillary plasma glucose: <180 mg/dL

A1C indicates glycosylated hemoglobin; AACE/ACE, American Association of Clinical Endocrinologists/American College of Endocrinology; ADA, American Diabetes Association; T2DM, type 2 diabetes mellitus.

ately prescribed physical activity), as well as diabetes education and self-management training for all patients.[16,20]

In some cases, these algorithms place somewhat different emphasis on certain medication classes, discussed below. Regardless of drug choice, the primary objective of each algorithm is to enable patients to reach the recommended glycemic target with as few adverse effects as possible. For example, when considering combination regimens, both the ADA/EASD and the AACE/ACE algorithms recommend selecting drug classes with complementary mechanisms of action, so as to ensure the broadest glucose-lowering effect. In addition, both algorithms stress the importance of advancing therapy expeditiously, in order to reach and maintain A1C goals.[7,11]

The ADA writing group's algorithm divides therapies into 3 steps with 2 tiers. Tier 1, which is recommended for the majority of patients with T2DM who do not need initial therapy with insulin, includes established, well-validated, cost-effective, single-agent or combination therapies including metformin, sulfonylureas, and insulin. Within tier 1, a stepwise approach to glycemic control begins with metformin (if there are no contraindications or intolerance), and then, if glycemic goals are not attained, adds a sulfonylurea or basal insulin, and then moves to an intensive insulin regimen plus lifestyle and usually metformin therapy. Within the stepwise model, the ADA advocates the earlier use of more effective glucose-lowering agents when A1C level is elevated (>8.5%)—for example, adding basal insulin, rather than a second oral agent, to metformin. The algorithm also notes that "In the setting of severely uncontrolled diabetes…defined as fasting plasma glucose (FPG) levels of at least 250 mg/dL, random glucose levels consistently higher than 300 mg/dL, A1C levels greater than 10%, or the presence of ketonuria, or very symptomatic diabetes with polyuria, polydipsia, and weight loss, insulin therapy in combination with lifestyle intervention is the initial treatment of choice."[11]

Tier 2 includes what the writing group refers to as less well validated agents, such as the GLP-1 receptor agonist exenatide or the TZD pioglitazone, added to metformin when non-A1C level benefits (ie, avoiding hypoglycemia, weight loss promotion) are important considerations. The TZD rosiglitazone was not included because of its potential association with increased risk for myocardial infarction. Patients who do not achieve their A1C goal with these agents should be advanced to basal and then intensive insulin, as outlined in tier 1. The ADA writing group did not include DPP-4 inhibitors (which at the time were relatively new) in tier 2 because of limited long-term safety data, although it was noted that these drugs may be appropriate in certain patients.[11]

The AACE/ACE writing group's algorithm first stratifies patients into treatment groups based on their initial A1C level (≤7.5%, 7.6%-9.0%, or >9.0%). They emphasize the desirability of agents with a low risk for hypoglycemia and weight gain. Patients with A1C levels of 7.5% or less should usually be started on metformin (unless contraindicated). However, a TZD may be preferred in patients with metabolic syndrome or nonalcoholic fatty liver disease, a GLP-1 receptor agonist or alpha-glucosidase inhibitor in patients with elevated PPG, and/or a DPP-4 inhibitor in patients with elevated PPG and FPG. If the A1C goal is not reached, metformin-based dual therapy (or, alternately, a TZD plus GLP-1 receptor agonist or DPP-4 inhibitor) should be used, followed by metformin-based triple therapy. The writing group recommends that patients with A1C levels in the range of 7.6% to 9.0% initiate treatment with metformin-based dual therapy, followed by metformin-based triple therapy. In both of these A1C groups, patients who do not reach their glycemic target should be started on insulin, with or without other agents. When A1C level is greater than 9.0%, previously treated or symptomatic drug-naïve patients should be started on insulin therapy (with or without other agents), while drug-naïve asymptomatic patients may be started on metformin-based triple therapy. For combination therapy across all A1C level groups, the AACE notes that the GLP-1 receptor agonist exenatide (liraglutide was not available during development of the most current algorithm) is preferred over DPP-4 inhibitors because of its impact on postprandial glucose excursions, body weight, satiety, and gastric emptying. In all patients,

A1C levels should be rechecked every 2 to 3 months, and treatment intensified until the glycemic target is achieved.[7]

Balanced against the benefits of optimal glycemic control, healthcare professionals and managed care organizations must consider the benefits, side effects, and tolerability of specific antihyperglycemic agents, as well as a patient's willingness and ability to adhere to a treatment plan.[11] Finally, it is to be expected that each patient will present with unique psychological, social, and economic circumstances, their own treatment preferences, and a system of values that must be incorporated into their personal treatment plan.[16,20]

Incretin-Related Agents: Some Highlights From the 2011 ADA Scientific Sessions

Because of the low risk for hypoglycemia and the association with weight neutrality (with DPP-4 inhibitors) or weight loss (with the GLP-1 receptor agonists), the use of incretin-related agents has an important role in the management of T2DM. A number of studies presented at the 2011 ADA Scientific Sessions covered incretin-related drugs currently approved for use in the United States; some studies demonstrated longer-term results with incretin-related compounds and some directly compared the GLP-1 receptor agonists liraglutide and exenatide against each other or versus the DPP-4 inhibitor sitagliptin.

In the 2009 LEAD-6 trial, Buse et al showed that, in patients previously treated with metformin and/or a sulfonylurea, the addition of liraglutide improved A1C levels more than exenatide, and was also associated with less hypoglycemia.[22] At the ADA meeting, Buse provided more data from an open-label extension study where patients receiving liraglutide continued with this treatment, but those on exenatide were switched to liraglutide. Of patients who reached ADA target with exenatide in the initial trial, 89% remained at target with liraglutide, and experienced a further 0.3% mean reduction in A1C level. For patients who failed to reach ADA target with exenatide, 32% were subsequently able to reach target with liraglutide 1.8 mg, with a mean 0.8% further reduction in A1C level after switching to liraglutide.[23]

In a study of a patient cohort already taking metformin, with mean baseline A1C levels just over 8%, the addition of liraglutide (1.2 or 1.8 mg/day) or sitagliptin (100 mg/day) for 52 weeks lowered A1C levels; however, switching to liraglutide during the follow-up phase further improved outcomes. After 52 weeks, 96% of patients entered a 26-week extension; of these, 91% (381 of 419 patients) completed the full 78 weeks. During the extension, patients given sitagliptin were switched to liraglutide 1.2 or 1.8 mg daily (via weekly dose escalations of 0.6 mg), while those given liraglutide continued unchanged for another 26 weeks. Treatment with sitagliptin (100 mg/day) for 52 weeks lowered A1C levels by a mean of 0.9%, and patients who switched from sitagliptin to liraglutide experienced further reductions in A1C levels (0.2%-0.5%, P <.01 for both) and were significantly more likely to achieve target A1C levels of less than 7% (30% for sitagliptin vs 50% for liraglutide). Patients who switched to liraglutide also experienced significant further reductions in FPG levels and body weight. In addition, patients who were given liraglutide (1.2 mg and 1.8 mg, respectively) for both the initial study period and the 26-week extension (for 78 weeks of continual liraglutide treatment) experienced reduced A1C levels (−0.9%, −1.3%), FPG levels (−1.3, −1.7 mmol/L), and more weight loss (−2.6, −3.1 kg) compared with baseline, with low rates of minor hypoglycemia (0.156, 0.130 events/patient-year).[24]

To assess the effect of switching from oral to injectable therapy, patients in this study were also evaluated at 52 and 78 weeks using the 8-question Diabetes Treatment Satisfaction Questionnaire.[25] Researchers found that the switch from sitagliptin to liraglutide was associated with improved patient satisfaction, despite the fact that subjects were changing to an injectable medication from an oral treatment. Respondents indicated that they would recommend this treatment option to other patients, and that they had a strong desire to continue receiving liraglutide.[26]

A study comparing liraglutide, exenatide, and sitagliptin in the context of background metformin or sulfonylurea use found that patients treated with the higher of 2 liraglutide doses (1.8 mg) were more likely to reach a composite end point of A1C level less than 7% and weight loss compared with other treatments. Significantly more patients receiving once-daily liraglutide 1.8 mg achieved the composite end point compared with those treated with once-daily liraglutide 1.2 mg (odds ratio [95% CI]: 1.66 [1.14-2.41]; P <.01), twice-daily exenatide 10 µg (2.10 [1.41-3.14]; P <.001), or once-daily sitagliptin 100 mg (5.70 [3.63-8.94]; P <.001). The liraglutide 1.8-mg group had an A1C level reduction of 1.3% and a body weight reduction of 3.0 kg, while the liraglutide 1.2-mg, exenatide 10-µg, and sitagliptin-100 mg groups had reductions of 1.1%/2.7 kg, 0.9%/2.3 kg, and 0.9%/0.8 kg, respectively.[27]

Another series of direct comparator studies presented at the ADA meeting evaluated the efficacy of the DPP-4 inhibitors saxagliptin and linagliptin alongside alternative treatment regimens. Two analyses of a 52-week trial with a 52-week extension phase compared the efficacy and safety

of saxagliptin 5 mg versus the sulfonylurea glipizide as add-on therapy for patients already receiving metformin.[28,29] In the first analysis, the randomized, multicenter, 52-week trial compared saxagliptin 5 mg/day with glipizide 5 to 20 mg/day in patients with baseline A1C levels of 7.0% to 8.5% already taking metformin. Investigators found that more patients receiving saxagliptin achieved the A1C target of less than 7.0% without hypoglycemia or weight gain (33% of patients given saxagliptin vs 15% given glipizide).[28] The second analysis looked at the 52-week, randomized controlled trial, as well as the subsequent 52-week extension phase (36% of initial patients completed the study). Baseline A1C levels were 7.7% for both cohorts, and investigators found that saxagliptin and glipizide were associated with similar reductions in A1C levels (-0.4% for both). However, patients treated with saxagliptin experienced lower rates of hypoglycemia (3.5% vs 38.4% with glipizide), less weight gain, and slower progressive rises in A1C levels over time compared with sulfonylurea treatment.[29]

Last, a 2-year double-blind trial evaluated the efficacy of adding linagliptin versus the sulfonylurea glimepiride to ongoing metformin therapy. The 2 groups experienced similar A1C level reductions (-0.4% for linagliptin, -0.5% for glimepiride); however, compared with glimepiride, patients taking linagliptin experienced less hypoglycemia and weight gain, and fewer cardiovascular events.[30]

A Renewed Look at Lifestyle Intervention

With the recent number of medications proposed to treat obesity that have failed to receive approval by the FDA,[31] the need for all patients with, or at risk for, T2DM to engage in lifestyle intervention is being further emphasized by clinicians, employers, and payers.

Both the ADA and the AACE/ACE recommend lifestyle modifications for patients with prediabetes and diabetes. Specifically, they endorse medical nutrition therapy for weight loss and dyslipidemia, twice-weekly strength training, and 150 minutes/week of moderate physical activity, such as walking, for weight reduction and glucose control. Smoking cessation is also advised. To reduce the risk of T2DM development in patients with prediabetes, both organizations also recommend that individuals who are overweight/obese and have prediabetes lose at least 7% of their body weight (based on findings from the Diabetes Prevention Program [DPP], described below).[16,20]

Promising new data have come from clinical trials focused on lifestyle modification. The 4-year results from the randomized, controlled, multicenter Look AHEAD (Action for Health in Diabetes) Study, presented at the 2011 ADA Scientific Sessions,[37,38] found that patients with T2DM who engaged in intensive lifestyle intervention (caloric restriction and exercise) achieved a cumulative 6.15% weight loss, versus 0.88% in the control group (these participants were provided with support and education only). Intensively treated patients also experienced significant improvements in A1C levels, blood pressure measurements, high-density lipoprotein cholesterol levels, and triglyceride levels.[38]

Emerging data also suggest that it will be feasible to implement a series of community-level replications of the DPP. Published in 2002,[39] the initial DPP trial found that a lifestyle intervention, consisting of a 16-week counseling series that

Lifestyle Intervention and Patient Education Resources

There are an increasing number of organizations dedicated to disseminating information (often on their Web sites) about the causes, prevention, treatment, and public health burden of diabetes.

The National Diabetes Education Program (NDEP; www.ndep.nih.gov or www.yourdiabetesinfo.org), provides evidence-based, culturally appropriate, and language-specific information about diabetes in order to translate research results into clinical practice, improve the treatment and outcomes for people with diabetes, promote early diagnosis, and prevent or delay the onset of type 2 diabetes.[32,33]

One NDEP resource, HealthSense (http://ndep.nih.gov/resources/diabetes-healthsense/index.aspx), formerly known as the Support for Behavior Change Resource, is an online library of more than 140 resources compiled by NDEP to help people with, or at risk for, diabetes to make successful, long-term lifestyle changes and to better adhere to any medications prescribed for them by their healthcare professionals.[34]

In addition, to help reduce the risk of development and progression of diabetic microvascular and macrovascular complications, and because of the important link between diabetes and CV disease, the NDEP encourages all patients to know and try to achieve goals for their A1C levels, blood pressure measurements, and cholesterol levels, or "ABCs of Diabetes" available at: http://ndep.nih.gov/i-have-diabetes/KnowYourABCs.aspx. [34,35]

The NDEP also has a number of resources to help in efforts to prevent the transition from prediabetes to diabetes. These include the "Small Steps. Big Rewards. Your GAME PLAN to Prevent Type 2 Diabetes Health Care Provider Toolkit" (http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=118) and "The Road to Health Toolkit" (http://ndep.nih.gov/publications/PublicationDetail.aspx?PubId=152), designed for African Americans and Hispanics/Latinos at risk for T2DM. The latter provides materials to start a community outreach program reinforcing the message that T2DM can be delayed or prevented.[33,36]

incorporated dietary and physical activity instruction, was associated with an average 5.6 kg weight loss at 3 years (with 50% of patients achieving a weight loss of approximately 7% of initial body weight). This intervention was also associated with a 58% reduction in progression from prediabetes to T2DM. When the study results were published, the authors estimated that there were approximately 10 million people living in the United States with weight and metabolic characteristics similar to the DPP participants. If these individuals could participate in such a program, they suggested, the incidence of T2DM in this population would decrease substantially.

Recently, 10-year follow-up data of the original DPP cohort were published. The DPP Outcomes Study followed participants for an additional 7 years, during which time lifestyle intervention and metformin participants were encouraged to continue those interventions and all participants were offered a modified lifestyle intervention. Eighty-eight percent of the original cohort continued in the study. Although patients in the original lifestyle group regained some of the weight they initially lost (approximately 5 kg), progression to diabetes in this group over time still remained 34% lower than in the placebo group, and 18% lower than in the metformin group.[40]

At the 2011 ADA Scientific Sessions, Herman and colleagues presented further data from the 10-year follow-up of the DPP, examining the 10-year cost-effectiveness of the DPP interventions for the primary prevention of T2DM. This study showed that over 10 years, from a payer perspective, both lifestyle intervention and metformin were less expensive and more effective than placebo. The direct medical costs of care outside the study increased over time for all groups, but were highest for placebo, while quality of life was better for the intensive lifestyle group.[41]

It is also important to note that a number of programs in community settings, such as the Young Men's Christian Association (YMCA), University of Pittsburgh Diabetes Prevention Support Center, and the Montana Diabetes Control Program, have successfully replicated the DPP results over the short term (from 3 to 12 months), at a lower cost than the original DPP program.[42-44] Currently, the US Centers for Disease Control is working with the YMCA and UnitedHealth Group to scale the DPP at multiple additional locations in over 20 states nationwide.[45] A report presented at the 2011 ADA Scientific Sessions described the randomization process (intervention vs standard advice) and participation/retention rates for a DPP adaptation program currently being conducted in Indianapolis, Indiana. In this program, nearly 500 overweight or obese (mean body mass index, 37.0 kg/m^2) adult patients with prediabetes, referred from 9 local primary care practices, have been successfully randomized to a DPP intervention. A large proportion of these participants are African American (57%), and the majority (73%) report an annual income of less than $25,000. The program is currently under way, with attendance rates of approximately 70%. The authors believe that their research indicates that it is feasible to implement community-based DPP programs in the context of a randomized controlled trial.[46]

Conclusion

The treatment landscape for T2DM has increased in complexity, even as the condition's incidence and prevalence have continued to grow. Metformin remains a cornerstone of therapy and other older, relatively inexpensive, and thoroughly investigated antihyperglycemic agents maintain popularity. However, some new treatment options offer glycemic efficacy along with other associated benefits. The incretin-based agents (DPP-4 inhibitors and GLP-1 receptor agonists) have the advantage of stimulating insulin release and suppressing glucagon secretion in a glucose-dependent manner, which should reduce the risk of hypoglycemia (unless these agents are given in combination with a sulfonylurea or insulin). Furthermore, they are not associated with weight gain like a number of conventional antihyperglycemic agents. To the contrary, the GLP-1 receptor agonists are very often associated with clinically significant weight loss. Long-term outcome studies for many newer therapies are needed, and are currently under way. Along with comparative effectiveness studies, these will help to refine future treatment algorithms and guidelines to support even better clinician choices, as well as managed care organizations' efforts to make the best treatment coverage decisions.

In addition, while T2DM treatments, both new and old, dominate the diabetes conversation, our understanding of the importance and feasibility of diabetes prevention is increasing. The long-term results of the DPP, along with the resources available from entities such as the ADA, AACE/ACE, and NDEP, show that lifestyle modification programs can work to prevent, or at least delay, the development of T2DM. Managed care organizations are increasingly recognizing the benefits of these diabetes prevention efforts.

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