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After reading this article, the physician should be better able to:

1. Summarize challenges and barriers to good glycemic control for patients with type 2 diabetes mellitus (T2DM)
2. Identify patients at risk for T2DM and implement appropriate screening strategies
3. Summarize lifestyle modification recommendations for patients with T2DM
4. Select treatment options for patients with T2DM based on disease pathophysiology and patient-specific characteristics
5. Develop individualized treatment goals for patients with T2DM

FACULTY DISCLOSURE STATEMENTS

Dr Cobble has disclosed that he is on the advisory boards and speakers bureaus for Abbott Laboratories, AstraZeneca, and Eli Lilly and Co. Dr. Cobble is on the speakers bureau for GlaxoSmithKline, Forest Laboratories, and CVTX.

Dr Peters has disclosed that she is on the advisory boards and speakers bureaus for Abbott Diabetes Care, Amylin, Eli Lilly and Co., Mini Med, Medtronic, Novo Nordisk, Inc., and Takeda Pharmaceuticals NA, Inc.

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STATEMENT OF SUPPORT

This program is sponsored by the Primary Care Education Consortium and is supported by an educational grant from Takeda Pharmaceuticals NA, Inc.

Medium: CME print publication

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Clinical practice in type 2 diabetes: After metformin and lifestyle, then what?

The challenge of type 2 diabetes mellitus

According to the most recent data from the Centers for Disease Control, nearly 24 million Americans have type 2 diabetes mellitus (T2DM); of these, 6 million individuals with T2DM remain undiagnosed. At least 57 million more American adults are at high risk for developing T2DM by virtue of having impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both, which constitute prediabetes.¹ Treating T2DM remains challenging, despite the availability of effective therapies. Recent data indicate that slightly more than half of the patients (~56%) with T2DM are achieving the American Diabetes Association (ADA) glycosylated hemoglobin (HbA1C) goal of <7%.² A major contributing factor to the inability to maintain glycemic control in patients with T2DM is its progressive nature. There is a continuum from normoglycemia to IGT/IFG (prediabetes) to diabetes, and from uncomplicated diabetes to more difficult-to-control diabetes and diabetes with complications. This continuum has implications for treatment strategies and for the need to continually modify these strategies as the disease progresses. Understanding

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This supplement to *The Journal of Family Practice* was supported by an educational grant from Takeda Pharmaceuticals North America, Inc., and was submitted by the Primary Care Education Consortium. It has been edited and peer reviewed by *The Journal of Family Practice*.

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EDITORIAL SUPPORT

Editorial support for the development of this supplement was provided by Primary Care Education Consortium.

Release Date: November 1, 2009
Expiration Date: November 1, 2010

METHOD OF PHYSICIAN PARTICIPATION

After reading the supplement in its entirety, go to: www.pceconsortium.org/JFPNov2009TK and complete the online evaluation and post-test. Upon completing the evaluation and passing the post-test you will be prompted to print your certificate of completion.

CLINICAL PRACTICE RECOMMENDATIONS FOR AAFP EB CME DESIGNATION

1. Practice Recommendation: Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, for microvascular disease prevention, the A1C goal for nonpregnant adults in general is <7%.

Evidence-Based Source: American Diabetes Association. Standards of medical care in diabetes—2009.

Volume/Issue/Page Number of Article of Supporting Evidence: Diabetes Care 2009;32(S1):S7.

Strength of Evidence: A. Consistent, good-quality patient-oriented evidence.

2. Practice Recommendation: In overweight and obese insulin-resistant individuals, modest weight loss has been shown to reduce insulin resistance. Thus, weight loss is recommended for all overweight or obese individuals who have or are at risk for diabetes.

Evidence-Based Source: American Diabetes Association. Standards of medical care in diabetes—2009.

Volume/Issue/Page Number of Article of Supporting Evidence: Diabetes Care 2009;32(S1):S7.

Strength of Evidence: A. Consistent, good-quality patient-oriented evidence.

3. Practice Recommendation: People with diabetes should be advised to perform at least 150 min/week of moderate intensity aerobic physical activity (50%-70% of maximum heart rate).

Evidence-Based Source: American Diabetes Association. Standards of medical care in diabetes—2009.

Volume/Issue/Page Number of Article of Supporting Evidence: Diabetes Care 2009;32(S1):S8.

Strength of Evidence: A. Consistent, good-quality patient-oriented evidence.



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where the patient is on the continuum of disease may help identify mechanisms of action that can be targeted and aid in therapeutic decision-making. For example, early in the disease process, T2DM is characterized by insulin resistance and hyperinsulinemia. As such, agents that target insulin sensitivity and insulin resistance may be especially useful early in the disease process. Although the 2 main defects of T2DM are insulin resistance and pancreatic β -cell dysfunction/failure (FIGURE 1), other aspects of its pathophysiology may be targeted to specific metabolic pathways and effects (FIGURE 2).

For decades, the standard treatment paradigm has been “treat to fail” rather than “treat to succeed.” Typically, therapeutic strategies started with diet and exercise, with the slow and sequential addition of drugs. However, the current treatment paradigm acknowledges that there are intrinsic physiologic defects early in the course of the disease that require efforts beyond lifestyle modification alone. When treatment goals are not achieved or maintained with metformin and lifestyle modification alone, treatment is quickly intensified to combination drug therapy and lifestyle change.³

The failure of drugs to maintain efficacy over time is another barrier to long-term treatment success. Medication “durability”—the ability to maintain glycemic control with a given agent over time—may be useful in therapeutic decision-making. Different classes of drugs appear to have different degrees of durability. A study of patients with newly diagnosed T2DM evaluated the effects of different classes of oral antihyperglycemic agents. The lowest 5-year failure rate of monotherapy was with the thiazolidinedione (TZD) rosiglitazone (15%); an intermediate failure rate was reported for metformin (21%); and the greatest inability to maintain control was associated with the sulfonylurea glyburide (34%).⁴

Adherence to diabetes therapies is a challenge if all risk factors (eg, glucose, blood pressure, lipids) are being addressed. However, according to one study, the number of medications taken by patients with diabetes was not associated with adherence (ie, the more medications a patient is taking does not necessarily result in poorer adherence). Adherence was significantly lower, however, when the value of the intervention was poorly understood.⁵ Potentially modifiable disease and medication beliefs associated with poor medication adherence among patients with T2DM include: (1) believing they have diabetes only when their blood glucose levels are high; (2) saying there is no need to take medicine when the glucose is normal; (3) worrying about side effects of diabetes medications; (4) lack of self-confidence in controlling diabetes; and (5) feeling that the medications are hard to take.⁶

Screening and diagnosis

Major risk factors for T2DM are obesity and family history of T2DM. Approximately one-third of adult Americans are considered obese.⁷ A family history of T2DM also predisposes individuals to developing T2DM. Other risk factors include a sedentary lifestyle, older age, unhealthy eating habits, as well as the presence of high blood pressure and elevated cholesterol levels. In women, a history of gestational diabetes, delivery of a baby over 9 lb, and polycystic ovary syndrome are risk factors for development of T2DM. Minorities are at greater risk for T2DM: African Americans, Native Americans, Hispanics, Asians, East Indians, and Pacific Islanders all have higher rates of T2DM than do Caucasians. The presence of any of these risk factors indicates that such individuals should be periodically screened for T2DM. In the absence of risk factors, patients older than age 40 should be screened for T2DM.⁸

The diagnosis of T2DM has typically been made when fasting plasma

glucose (FPG) is >126 mg/dL; when symptoms of hyperglycemia are present; and when a random plasma glucose is ≥ 200 mg/dL or a 2-hour plasma glucose level is ≥ 200 mg/dL during a 75-g oral glucose tolerance test. Now, an HbA1C value $\geq 6.5\%$ can also be used for the diagnosis of diabetes (<http://forecast.diabetes.org/news/international-expert-committee-recommends-new-way-diagnose-diabetes-a1c-test-recommended-tool-d>).

Lifestyle modification

Lifestyle modification is an integral part of the management of T2DM. Family physicians should inquire about food habits and physical activity at each patient visit. The emphasis of medical nutritional therapy should be on control of blood glucose rather than just on weight loss.

Education should focus on carbohydrates, with respect to portion size and the number of servings per meal. Additionally, more refined carbohydrates should be replaced with higher fiber carbohydrate choices. A diet composed of complex carbohydrates (50%-55%), protein (20%-25%), and healthy fats (20%) is crucial. Saturated fat intake should be <7% of total calories, with minimal trans fat intake. Carbohydrate counting may be an important aspect of diabetes therapy that can be addressed by a dietitian, particularly for patients taking insulin. Alcohol use should not exceed moderate intake (≤ 1 drink women, ≤ 2 drinks for men per day).⁸ If blood glucose monitoring is used, food records also should be maintained to detect cause-and-effect patterns.

Physical activity should always be encouraged. Physical activity should include at least 150 minutes per week of aerobic physical activity, which may be as simple as walking at a brisk pace. Some exercise is better than none. Patients should be screened for the presence of cardiovascular disease (CVD) and other complications before embarking on a higher intensity exercise regimen. In the absence of contraindications, resistance training 3 times per week is also recommended.⁸ The expertise of, and assistance from, health care professionals with appropriate training and experience with behavioral modification are recommended to enhance the success of lifestyle modification efforts. Such

FIGURE 1
Type 2 diabetes pathogenesis

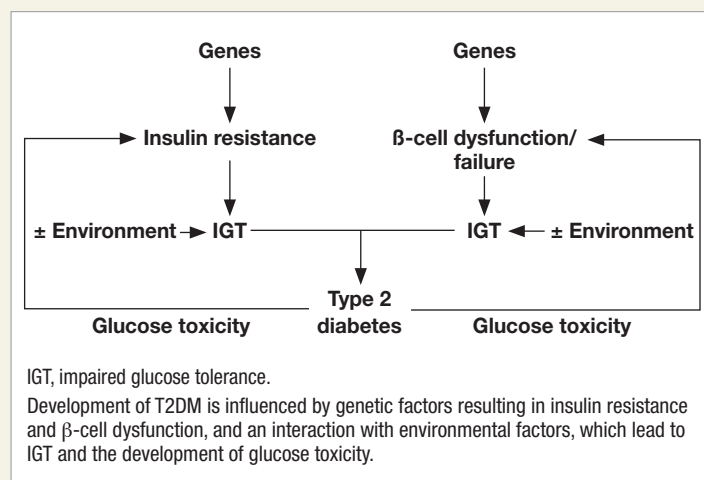
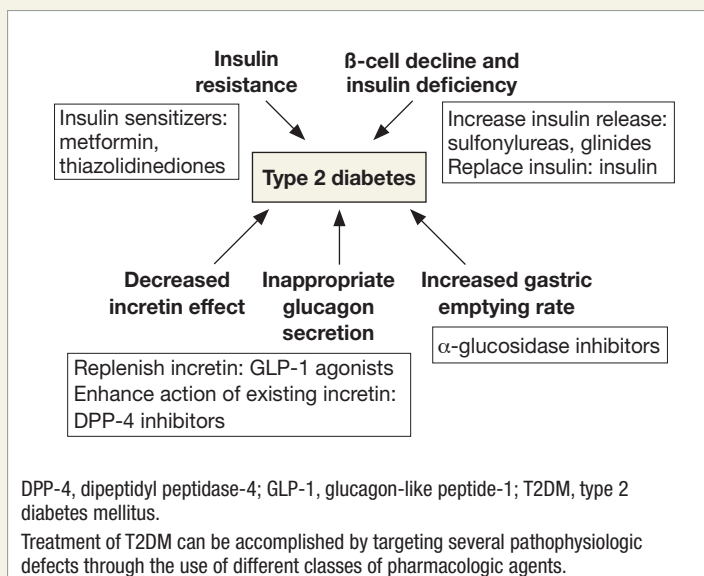


FIGURE 2
Approaches to T2DM based on pathophysiologic defects



individuals are often registered dietitians and/or diabetes educators.

Helpful resources regarding medical nutritional therapy may also be found at the ADA website (<http://www.diabetes.org/food-nutrition-lifestyle/nutrition.jsp>); the National Diabetes Education Program website (<http://www.ndep.nih.gov/>); and in the American Association of Clinical Endocrinologists' "Power of Prevention Guide to Physical Activity" (http://www.powerofprevention.com/popguide/FINAL_POP_Book.pdf).

TABLE 1
ADA-recommended glycemic targets for T2DM

Measurement	Normal	Goal
Preprandial	<100 mg/dL	90-130 mg/dL
Postprandial (2 hour)	<140 mg/dL	<180 mg/dL ^a
HbA1C	<6.0%	<7.0% ^b

ADA, American Diabetes Association; HbA1C, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus.

^aPeak value.

^bIn general, although recently diagnosed patients may benefit from near normal HbA1C goals, patients with severe comorbidities may need less stringent HbA1C goals.

Establishing reasonable and relevant treatment goals

Priorities for care of patients with T2DM can be summarized in the abbreviation *ABC*: (A) glucose control as measured by HbA1C; (B) Blood pressure control; and (C) attention to normalizing Cholesterol profiles. Multifactorial intervention with both pharmacotherapy and lifestyle modification targeted at these ABCs has been shown definitively to reduce the risk of mortality in patients with T2DM.⁹

Glucose control can also be considered in the context of ABCs, that is, (A) glucose levels After meals (postprandial glucose [PPG]); (B) Before meals (FPG); and (C) the Constant or average glucose levels (HbA1C). Without targeting A–after meal glucose, B–before meal glucose, and C–constant 24-hour glucose, it will be difficult to achieve HbA1C control.

These goals are summarized in **TABLE 1**.⁸ The ADA HbA1C goal for patients with diabetes is <7%, with the target being as close to normal as possible without risking hypoglycemia. Less stringent goals may be appropriate for some patients, specifically those with 1 or more of the following: (1) a history of severe hypoglycemia; (2) limited life expectancy; (3) advanced microvascular or macrovascular complications; or (4) extensive comorbid conditions (or those with long-standing diabetes for whom the general goal is difficult to attain). Conversely, lower HbA1C goals (ie, <7%) may be appropriate for patients with a short duration of diabetes and long life expectancy, but without significant CVD.⁸ Overall it is important to individualize targets—for one person with existing CVD, stringent lipid and blood pressure targets may be appropriate, while glycemic targets may need to be relaxed; for another person without CVD and a short duration of disease, very stringent glucose targets may be most appropriate.

Considerations when initiating diabetes therapy

Patient education and patient self-management are critical to the success of any diabetes treatment strategy.

Empowered patients are more successful patients. Diabetes educators, nurses, and other trained staff members can assist in educating patients about key aspects of diabetes care (eg, the need for foot self-examinations; yearly tests, such as eye examinations; signs and symptoms of hypoglycemia and hyperglycemia) and provide guidance on interpretation of self-monitoring of blood glucose. Dietitians are skilled in behavior modification and can provide valuable support regarding lifestyle modifications. Many pharmacists are also trained in motivating patients and educating them about their medications. Group classes to teach certain skills, such as insulin or injectable medication administration techniques or insulin pump management, can reduce the burden on a given physician.

Consideration of disease duration and the degree of HbA1C lowering that is required to bring patients to their individual goals may guide treatment decisions. **TABLE 2** (available online only, at www.jfponline.com) delineates the effect of available classes of agents on HbA1C, FPG, or PPG, the mechanisms of action, the administration route(s), common or serious adverse effects, monitoring issues, and relative costs.

Starting pharmacotherapy

The 2009 ADA/European Association for the Study of Diabetes (EASD) treatment algorithm³ for the management of hyperglycemia in patients with T2DM represents the most recent update, taking into account both information on the safety and efficacy of agents for which there is considerable clinical experience (tier 1), and the availability of relatively new agents (tier 2) that work by other, complementary mechanisms of action.³ An ADA consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication, but does not represent official association opinion. The goal of therapy is to achieve and maintain HbA1C goals and to promptly change interventions as rapidly as medication titration can be implemented when target goals are not being achieved.

Step-1 therapy: Well established

Lifestyle interventions, such as weight loss, can have important effects on glucose control as well as on blood pressure and dyslipidemia. The obvious limitation to lifestyle modification is the ability of patients to adhere to regimens over the long-term. Metformin has become a cornerstone of therapy based on its efficacy, low risk of hypoglycemia, low risk of weight gain, and generic availability. The ADA/EASD treatment algorithm recommends its use, along with lifestyle modification, as the initial therapeutic strategy for patients with T2DM.³

Metformin is generally well tolerated; the most common side effects are gastrointestinal. There are certain contraindications to the use of metformin, severe renal dysfunction (estimated glomerular filtration rate <30 mL/min) being among the most important. Low-dose metformin (500 mg) once or twice a day, or 850 mg once a day, with food is recommended as a starting point; if tolerated, the dose can be advanced to 850 to 1000 mg twice a day, making dosage adjustments in 1- to 2-week intervals until a maximum dose of 2000 mg is achieved. Titration to a maximum dose over 1 to 2 months as tolerated is recommended.³

Step-2 therapy: Combination therapy treatment strategies for T2DM

Tier-1 recommendations for step-2 therapy include the addition of either a sulfonylurea or basal insulin to metformin and lifestyle modification.³ This approach focuses on increasing insulin supplies to the tissue, either by enhancing secretion (sulfonylureas) or by providing exogenous supplementary insulin. These 2 classes of drugs have been available for the treatment of diabetes for many decades and, thus, a significant body of clinical experience exists.

Hypoglycemia is the major concern with the use of either sulfonylureas or insulin. The use of sulfonylureas results in a relatively rapid lowering of glucose levels; however, their use is not always successful in maintaining glucose control over the long-term.⁴ Progressive β -cell failure results in eventual loss of efficacy because sulfonylureas depend on functioning β -cells and, therefore, are ineffective in the absence of insulin-producing capacity.

Compared to older sulfonylureas, second-generation agents (ie, gliclazide, glimepiride, glipizide) are preferred because of their lower risk of hypoglycemia. Glycemic benefits of sulfonylureas are realized at approximately half their maximal doses, although in some, increasing to maximum doses may be helpful. Low-dose short-acting glipizide can be used before meals in patients who develop hypoglycemia on long-acting drugs or who have renal impairment. Weight gain of approximately 2 kg is not uncommon after initiation of sulfonylurea therapy.³ Generic availability of sulfonylureas represents an economic advantage to their use.

Insulin has no lower limit of glucose-lowering ability (eg, there is no maximum dose beyond which a therapeutic effect will not occur, although in some insulin-resistant patients very high doses are required). Insulin remains the most potent glucose-lowering agent available.³ In clinical practice, however, patients with T2DM on insulin therapy often have higher A1C levels than patients on oral agents, and in the large United Kingdom Prospective Diabetes Study, patients on insulin therapy had a gradual increase in HbA1C levels¹⁰ despite the “infinite” glucose-lowering

ability of insulin. Because of multiple barriers, such as hypoglycemia and the need for patients to adjust doses, monitor blood glucose levels, and self-inject, insulin is often difficult to use well in primary care.

Basal insulin in the form of NPH is generically available; however, NPH is not a “true” long-acting insulin but is, in reality, an intermediate-acting insulin. The advent of long-acting insulin analogues, with more predictable and physiologic profiles, is associated with less risk of hypoglycemia than the older, human regular or NPH insulins.¹¹ Cost considerations, however, may limit patient access.

The use of once-daily basal insulin is the simplest strategy for initiating insulin therapy in appropriate patients. Insulin therapy is often associated with weight gain and, like sulfonylureas, the most important side effect is the risk of hypoglycemia. Patients with lifestyles and jobs that pose a greater risk during hypoglycemic episodes (eg, construction work, factory work, occupations that require extensive driving) may not be candidates for insulin therapy. Both insulin and sulfonylurea therapy are based on a “fix fasting (plasma glucose) first” approach.

Insulin should be considered for patients with severe hyperglycemia and is, in fact, recommended as first-line therapy for patients with HbA1C levels of approximately 10%; it may also be warranted for patients with HbA1C levels >8.5%, in whom the use of another oral agent may not result in sufficient glucose-lowering.³ While finer needles and insulin pen delivery devices have made self-administration of insulin less onerous, there may be initial hesitation on the part of both physicians and patients about using insulin as step-2 therapy for patients with lesser glucose-lowering requirements.

Other options (tier 2) for combination therapy when metformin and lifestyle prove inadequate include the oral TZD pioglitazone or the injectable glucagon-like peptide 1 (GLP-1) agonist exenatide.³ Pioglitazone and exenatide are recommended specifically when hypoglycemia is particularly undesirable (eg, for patients with hazardous jobs) and/or when weight gain is a significant concern.³ TZDs target insulin resistance and thus are appropriate for use in patients who still have insulin secretory ability (eg, those with a relatively short duration of disease). TZDs also have effects on PPG levels. A TZD-metformin-based therapy has been shown recently to be associated with greater improvements in insulin resistance-related parameters compared with a sulfonylurea-metformin-based regimen.¹² There is robust published clinical trial evidence demonstrating that TZDs decrease the likelihood of progression from prediabetes to diabetes through preservation of β -cell function, including findings from DREAM,¹³ TRIPOD,¹⁴ and PIPOD.¹⁵

In clinical trials, TZD therapy is associated with less hypoglycemia and fewer withdrawals due to lack of efficacy or adverse events compared with sulfonylurea therapy.¹⁶ Early use (ie, within 6 months of a diagnosis of T2DM) of combination therapy with metformin plus pioglitazone resulted in a slower deterioration in glycemic control compared with metformin plus a sulfonylurea or a glinide.¹⁷ A recent meta-analysis comparing the addition of TZDs vs the GLP-1 agonist exenatide (discussed in more detail below) with oral agents revealed that TZDs produce greater improvements in glycemic control, while exenatide has the benefit of reducing body weight.¹⁸

After the publication of a meta-analysis in 2007 that concluded that there was an increased risk of CVD and myocardial infarction (MI) for patients using rosiglitazone,¹⁹ the Food and Drug Administration requested a boxed warning for both TZDs on the market—rosiglitazone and pioglitazone. The box warning was similar for both pioglitazone and rosiglitazone in terms of an increased risk for congestive heart failure (CHF). An additional box warning was added to rosiglitazone about the potential for an increase in CVD events. This was not added to pioglitazone.

However, there were some methodological flaws in this meta-analysis, primarily based on selection of studies.²⁰ A subsequent meta-analysis of TZDs did not support a CVD risk with TZDs,²¹ nor did a meta-analysis specifically of pioglitazone data, other than the well-known risk of CHF.²² Studies such as RECORD show no increase in CVD death or all-cause death with rosiglitazone.²³

Pioglitazone does differ from rosiglitazone in terms of the effects on lipids. In a head-to-head trial comparing rosiglitazone and pioglitazone in patients with T2DM and dyslipidemia, the group treated with pioglitazone had significant improvements in triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) particle concentration, and LDL particle size.²⁴ Data with pioglitazone confirm cardiovascular (CV) safety^{25,26} and benefit on CV markers such as blood pressure, lipids, inflammatory markers, carotid intima-media thickness, and intravascular ultrasound measures of plaque progression.²⁷⁻²⁹

TZDs do increase the risk for CHF and are contraindicated in patients with a history of CHF. Physicians should carefully monitor patients for signs and symptoms of CHF, including edema, dyspnea, and rapid weight gain. Swelling and edema are common side effects, which may contribute to the weight gain seen with this class of therapy. The risk of edema may be less with pioglitazone (odds ratio [OR], 2.42; confidence interval [CI], 1.90-3.08) than with rosiglitazone (OR, 3.75; CI, 2.70-5.20).³⁰

Recent evidence suggests that the long-term use of TZDs may reduce bone mineral density and result in a

2-fold increase in the risk of distal fractures in women and men (new data) with T2DM.^{31,32} Risk of hip or spine fractures is not increased. A bone density scan and measurements of vitamin D before initiating therapy may be appropriate in women, particularly those who are postmenopausal.

The other tier-2 option for step-2 therapy is the use of the GLP-1 agonist exenatide.³ Exenatide, the first of a new class of injectable agents, works by several mechanisms, some of which may be more relevant early in the course of diabetes (ie, impaired incretin response, suppressed glucagon secretion), as well as by increasing insulin secretion. GLP-1 agonists work in a glucose-dependent fashion and, therefore, are associated with a low risk of hypoglycemia. They appear to have durable glucose-controlling ability and are associated with weight loss (~5 kg over 20 months), in part because they increase satiety and slow gastric motility. They also are associated with clinically significant improvements in CV risk factors.³³ Short-acting exenatide primarily controls PPG excursions. Nausea and vomiting are the main adverse effects; these effects can be reduced by gradual dose escalation.³⁴

While there have been reports of pancreatitis with exenatide,³⁵ analysis of data from a large database has shown that all patients with diabetes are susceptible to pancreatitis and that there is no difference between the incidence of pancreatitis in patients starting incretin-based therapies vs metformin and glyburide.³⁶ However, patients should be advised to report cases of severe abdominal pain or vomiting to their physicians and physicians should consider therapies other than exenatide for patients with a history of pancreatitis.

Other agents

Other classes of antihyperglycemic agents are available that are not included in tier 1 or tier 2 of the current ADA/EASD treatment algorithm. These include amylin agonists (ie, pramlintide), alpha-glucosidase inhibitors, glinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors. One reason they are not included in the 2 tiers of preferred agents is their lower or equivalent overall glucose-lowering effectiveness. Additionally, some are less well proven (because they are newer on the market). However, they may be appropriate for specific patients. Other agents, such as the bile acid sequestrant, colesevelam, and bromocriptine, which acts on dopamine receptors, are so new to the diabetes treatment armamentarium that they have not yet been considered for published algorithms. The pros and cons of these agents will be reviewed briefly here.

Pramlintide is an injectable agent that is an analog of amylin, the small peptide hormone released by β -cells

into the bloodstream with insulin after meals. Like insulin, amylin deficiency occurs in patients with diabetes. By augmenting endogenous amylin, pramlintide aids in the absorption of glucose by slowing gastric emptying, promoting satiety via hypothalamic receptors (a different mechanism than for GLP-1 agonists) and by inhibiting inappropriate glucagon secretion. Pramlintide is approved for use as adjunctive therapy with regular insulin or with rapid-acting insulin analogs. It is administered 3 times daily via subcutaneous injection. Like GLP-1 agonists, its main side effects are gastrointestinal.³

Alpha-glucosidase inhibitors are another class of oral agents, which work by affecting gastrointestinal emptying. They are weight neutral, but are associated with gastrointestinal side effects, and require dosing 3 times per day.³ In addition, they are not available in generic form.

Glinides are oral agents that work by a similar mechanism as the sulfonylureas. They are rapidly effective and can lower HbA1C by up to 1.5 percentage points. They are associated with some risk of hypoglycemia and weight gain, and can be expensive.³

Like exenatide, DPP-4 inhibitors (eg, sitagliptin and saxagliptin) target the incretin system. However, unlike GLP-1 agonists, which provide supraphysiologic replacement of GLP-1, DPP-4 inhibitors work by preventing degradation of existing GLP-1, thus relying on the presence of physiologic GLP-1. In clinical trials, their glucose-lowering ability has been less than that of GLP-1 agonists. The advantages of the DPP-4 inhibitors include their oral, once-daily administration and a low risk of hypoglycemia. They may be best employed early in the T2DM disease process, before substantial impairments in incretin secretion become apparent. DPP-4 inhibitors are weight neutral, and are extremely well tolerated, with a side effect profile similar to placebo. DPP-4 inhibitors may also be useful in elderly patients unless they have severe or end-stage renal disease.³⁷

Colesevelam is an oral agent that has indications for adjunctive therapy both for glucose lowering in T2DM and for lipid lowering in patients with dyslipidemia. Its mechanism of action with regard to hypoglycemic effects is not well understood. As part of add-on therapy to many antihyperglycemic agents, colesevelam treatment results in an average additional 0.5% reduction in HbA1C levels.³⁸⁻⁴¹ In these trials, colesevelam was generally well tolerated. Colesevelam may be especially useful as adjunctive therapy for patients with comorbid dyslipidemia, a common finding in patients with T2DM. In patients also receiving glyburide or thyroid hormones, colesevelam should be administered 4 hours later.

The FDA recently approved bromocriptine mesylate for use in treating T2DM. Bromocriptine, either as monotherapy or adjunctive therapy to sulfonylurea or

insulin, reduces HbA1C levels relative to placebo by 0.55-1.2 percentage points. Bromocriptine therapy also reduces plasma triglycerides and free fatty acids by approximately 25% and 20%, respectively, among those also receiving sulfonylurea therapies.⁴² There is limited efficacy data in combination with TZDs and efficacy of bromocriptine has not been confirmed in combination with insulin. It should not be used in nursing women or in patients receiving ergot alkaloids.

Step-3 therapy

After combination therapy with 2 agents, what therapeutic choices remain? The options recommended in the ADA/EASD treatment algorithm include triple oral therapy (ie, metformin, pioglitazone, and a sulfonylurea) or the use of metformin with intensive insulin therapy (ie, basal and prandial insulin).³ There is, in fact, limited clinical trial data evaluating triple oral therapy, but this approach attempts to target several mechanisms of glucose lowering in patients with T2DM. Triple oral therapy may not be effective for patients who require more than a 1% decrease in HbA1C levels; it may also be less cost-effective.⁴³ This regimen also relies on residual β -cell function to be effective and therefore may not be logical for patients with long-standing diabetes. However, triple oral therapy may be associated with less hypoglycemia and improved HDL cholesterol levels than addition of NPH insulin to patients inadequately controlled by metformin and sulfonylurea therapy, and may be effective even in patients with HbA1C levels $>8\%$.⁴⁴ Once again, patient-specific characteristics and considerations will influence the choice of therapy.

In patients with a long history of diabetes, β -cell function may be substantially impaired, and the use of therapies such as insulin replacement may be most effective. All patients with T2DM should be educated about the progressive nature of the disease at the time of diagnosis and the need to adjust and change therapies over time, including the very real possibility that insulin will be needed at some point, through no fault of the patient. Physiologic insulin replacement requires provision of both basal and prandial insulin to address FPG and PPG. Basal and prandial insulin replacement may be achieved through the use of 1, 2, or 3 injections of premixed insulin⁴⁵ or through the use of multiple daily injections (eg, 1 injection of basal long-acting insulin in the evening or bedtime, and injections of rapid-acting insulin before meals). Active titration of insulin doses can ensure achievement of treatment goals.

Conclusions

Matching disease pathophysiology and patient-specific characteristics to therapeutic choices can improve

treatment success for patients with T2DM. Understanding the role of β -cell dysfunction and insulin resistance helps in selecting the right agent at the appropriate time. It is important to diagnose patients early and treat them progressively from the start. We now have many therapeutic agents with which to manage T2DM. Working with patients to understand their needs and concerns is critical as is educating them about premeal and after meal glucose changes. The role of lifestyle modification, such as proper

nutrition and activity, needs to be constantly reinforced with a simple message at each visit. Finally, explaining diabetes as a dynamic process can help patients understand the need to modify therapy over time. ■

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